10/520621

Azolidinone-vinyl fused-benzene derivatives

Field of the invention

This present invention is related to the use of azolidinone-vinyl fused-benzene derivatives of formula (I) for the treatment and/or prophylaxis of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, graft rejection or lung injuries. Specifically, the present invention is related to substituted azolidinone-vinyl fused-benzene derivatives for the modulation, notably the inhibition of the activity or function of the phospho-inositide-3'OH kinase family, PI3K, particularly of the PI3Kγ.

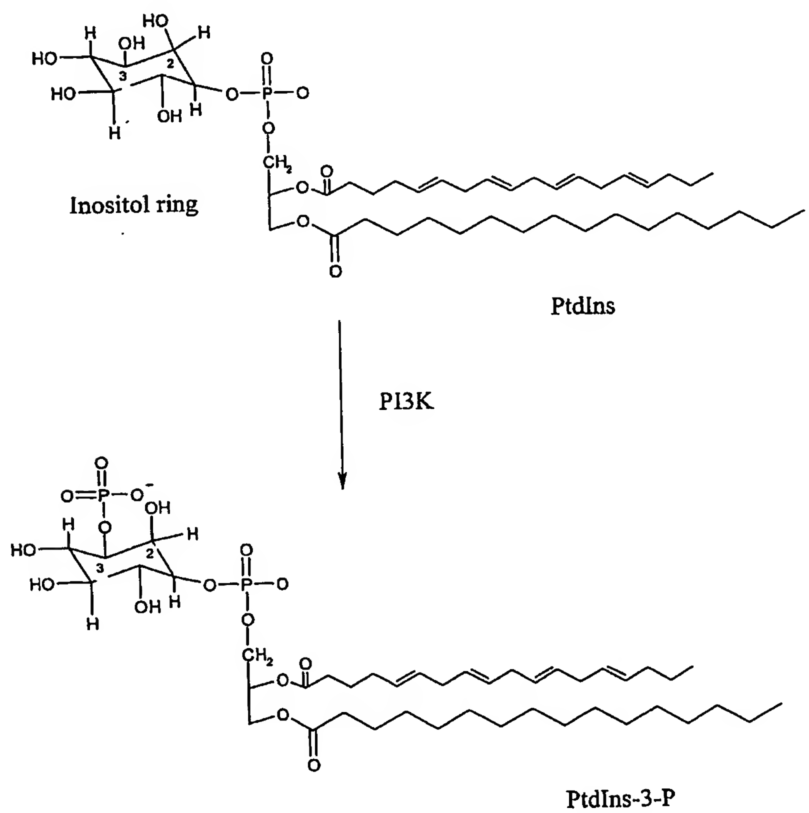
Background of the invention

Cellular plasma membranes can be viewed as a large store of second messenger that can be enlisted in a variety of signal transduction pathways. As regards function and regulation of effector enzymes in phospholipid signalling pathways, these enzymes generate second messengers from the membrane phospholipid pool (class I PI3 kinases (e.g. PI3Kgamma)) are dual-specific kinase enzymes, means they display both: lipid kinase (phosphorylation of phospho-inositides) as well as protein kinase activity, shown to be capable of phosphorylation of other protein substrates, including auto-phosphorylation as intra-molecular regulatory mechanism. These enzymes of phospholipid signalling are activated in response to a variety of extra-cellular signals such as growth factors, mitogens, integrins (cell-cell interactions) hormones, cytokines, viruses and neurotransmitters such as described in Scheme 1 hereinafter and also by intra-cellular cross regulation by other signaling molecules (cross-talk, where the original signal can activate some parallel

pathways that in a second step transmit signals to PI3Ks by intra-cellular signaling events), such as small GTPases, kinases or phosphatases for example.
The inositol phospholipids (phosphoinositides) intracellular signalling pathway begins with binding of a signalling molecule (extracellular ligands, stimuli, receptor dimerization, transactivation by heterologous receptor (e.g. receptor tyrosine kinase)) to a G-protein linked transmembrane receptor integrated into the plasma membrane.
PI3K converts the membrane phospholipid PIP(4,5)2 into PIP(3,4,5)3 which in turn can be further converted into another 3' phosphorylated form of phosphoinositides by 5'-specific phospho-inositide phosphatases, thus PI3K enzymatic activity results either directly or indirectly in the generation of two 3'-phosphoinositide subtypes that function as 2nd messengers in intra-cellular signal transduction (*Trends Biochem Sci.* **22(7)** p.267-72 (1997) by Vanhaesebroeck B et al., *Chem Rev*. **101(8)** p.2365-80 (2001) by Leslie N.R et al (2001); *Annu Rev Cell Dev Biol.* **17** p.615-75 (2001) by Katso R. et al. and *Cell Mol Life Sci*. **59(5)** p.761-79 (2002) by Toker a. et al.). Multiple PI3K isoforms categorized by their catalytic subunits, their regulation by corresponding regulatory subunits, expression patterns and signaling-specific functions (p110α, β, δ, and γ) perform this enzymatic reaction (*Exp Cell Res*. 25(1) p.239-54 (1999) by Vanhaesebroeck B. and *Annu Rev Cell Dev Biol*. **17** p.615-75 (2001) by Katso R. et al).

The evolutionary conserved isoforms p110 α and β are ubiquitiously expressed, while δ and γ are more specifically expressed in the haematopoetic cell system, smooth muscle cells, myocytes and endothelial cells (*Trends Biochem Sci.* **22(7)** p.267-72 (1997) by Vanhaesebroeck B et al.). Their expression might also be regulated in an inducible manner depending on the cellular-, tissue type and stimuli as well as disease context.
To date, eight mammalian PI3Ks have been identified, divided into three main classes (I, II, and III) on the basis of sequence homology, structure, binding partners, mode of activation, and substrate preference *in vitro*. Class I PI3Ks can phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate, and phosphatidylinositol-4,5-biphosphate (PIP2) to produce phosphatidylinositol-3-phosphate (PIP), phosphatidylinositol-3,4-biphosphate, and

phosphatidylinositol-3,4,5-triphosphate, respectively. Class II PI3Ks phosphorylate PI and phosphatidylinositol-4-phosphate. Class III PI3Ks can only phosphorylate PI (*Trends Biochem Sci.* **22(7)** p.267-72 (1997) by Vanhaesebroeck B et al, *Exp Cell Res*. 25(1) p.239-54 (1999) by Vanhaesebroeck B. and *Chem Rev*. **101(8)** p.2365-80 (2001) by Leslie N.R et al (2001)) G-protein coupled receptors mediated phosphoinositide 3'OH-kinase activation via small GTPases such as Gβγ and Ras, and consequently PI3K signaling plays a central role in establishing and coordinating cell polarity and dynamic organization of the cytoskeleton - which together provides the driving force of cells to move.



Scheme 1

As above illustrated in Scheme 1, Phosphoinositide 3-kinase (PI3K) is involved in the phosphorylation of Phosphatidylinositol (PtdIns) on the third carbon of the inositol ring. The phosphorylation of PtdIns to 3,4,5-triphosphate (PtdIns(3,4,5)P_3), PtdIns(3,4)P_2 and PtdIns(3)P act as second messengers for a variety of signal transduction pathways, including those essential to cell proliferation, cell differentiation, cell growth, cell size, cell survival, apoptosis, adhesion, cell motility, cell migration, chemotaxis, invasion, cytoskeletal rearrangement, cell shape changes, vesicle trafficking and metabolic pathway (*Annu Rev Cell Dev Biol.* **17** p.615-75 (2001) by Katso et al. and *Mol Med Today* **6(9)** p.347-57 (2000) by Stein R.C). Chemotaxis – the directed movement of cells toward a concentration gradient of chemical attractants, also called chemokines is involved in many important diseases such as inflammation/auto-immunity, neurodegeneration, angiogenesis, invasion/metastisis and wound healing (*Immunol Today* **21(6)** p.260-4 (2000) by Wyman NP et al.; *Science* **287(5455)** p.1049-53 (2000) by Hirsch et al.; *FASEB J* **15(11)** p.2019-21 (2001) by Hirsch et al. and *Nat Immunol.* **2(2)** p.108-15 (2001) by Gerard C. et al.).

Recent advances using genetic approaches and pharmacological tools have provided insights into signaling and molecular pathways that mediate chemotaxis in response to chemoattractant activated G-protein coupled receptors PI3-Kinase, responsible for generating these phosphorylated signalling products, was originally identified as an activity associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylates phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou et al., *Trends Cell Biol.* **2** p.358-60 (1992)). However, more recent biochemical studies revealed that, class I PI3 kinases (e.g. class IB isoform PI3Kγ) are dual-specific kinase enzymes, means they display both: lipid kinase (phosphorylation of phospho-inositides) as well as protein kinase activity, shown to be capable of phosphorylation of other protein as substrates, including auto-phosphorylation as intra-molecular regulatory mechanism.

So, PI3-kinase activation, therefore, is believed to be involved in a range of cellular responses including cell growth, differentiation, and apoptosis (Parker et al., *Current Biology*, **5** p.577-99 (1995), Yao et al., Science , **267** p.2003-05 (1995)).

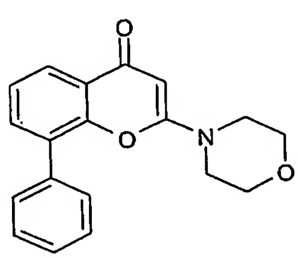
PI3-kinase appears to be involved in a number of aspects of leukocyte activation. A p85-associated PI3-kinase activity has been shown to physically associate with the cytoplasmic domain of CD28, which is an important costimulatory molecule for the activation of T-cells in response to antigen (Pages et al., *Nature*, **369** p,327-29 (1994); Rudd, *Immunity* **4** p.527-34 (1996)). Activation of T cells through CD28 lowers the treshold for activation by antogen and increases the magnitude and duration of the proliferative response. These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (Fraser et al., *Science*, **251** p.313-16 (1991)). Mutation of CD28 such that it can longer interact with PI3-kinase leads to a failure to initiate IL2 production, suggesting a critical role for PI3-kinase in T cell activation.

PI3Kγ has been identified as a mediator of G beta-gamma-dependent regulation of JNK activity, and G beta-gamma are subunits of heterotrimeric G proteins (*J. Biol. Chem.* **273(5)** p.2505-8 (1998). Cellular processes in which PI3Ks play an essential role include suppression of apoptosis, reorganization of the actin skeleton, cardiac myocyte growth, glycogen synthase stimulation by insulin, TNFα-mediated neutrophil priming and superoxide generation, and leukocyte migration and adhesion to endothelial cells.

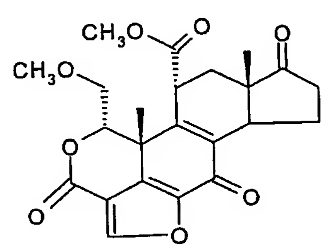
Recently, (*Immunity* **16(3)** p.441-51 (2002)) it has been described that PI3Kγ relays inflammatory signals through various G(i)-coupled receptors and its central to mast cell function, stimuli in context of leukocytes, immunology includes cytokines, chemokines, adenosines, antibodies, integrins, aggregation factors, growth factors, viruses or hormones for example (*J.Cell. Sci.* **114(Pt 16)** p.2903-10 (2001) by Lawlor MA et al., *Immunity* **16(3)** p.441-51 (2002) by Laffargue M. et al. and *Curr.Opinion Cell Biol.* **14(2)** p.203-13 (2002) by Stephens L. et al.).

Specific inhibitors against individual members of a family of enzymes provide invaluable tools for deciphering functions of each enzyme. Two compounds, LY294002 and

wortmannin (cf.hereinafter), have been widely used as PI3-kinase inhibitors. These compounds are non-specific PI3K inhibitors, as they do not distinguish among the four members of Class I PI3-kinases. For example, the IC_{50} values of wortmannin against each of the various Class I PI3-kinases are in the range of 1-10 nM. Similarly, the IC_{50} values for LY294002 against each of these PI3-kinases is about 15-20 µM (Fruman et al., *An. Rev. Biochem.*, **67** p.481-507 (1998)), also 5-10 microM on CK2 protein kinase and some inhibitory activity on phospholipases. Wortmannin is a fungal metabolite which irreversibly inhibits PI3K activity by binding covalently to the catalytic domain of this enzyme. Inhibition of PI3K activity by wortmannin eliminates the subsequent cellular response to the extracellular factor. For example, neutrophils respond to the chemokine fMet-Leu-Phe (fMLP) by stimulating PI3K and synthesizing PtdIns (3, 4, 5)P_3. This synthesis correlates with activation of the respirators burst involved in neutrophil destruction of invading microorganisms. Treatment of neutrophils with wortmannin prevents the fMLP-induced respiratory burst response (Thelen et al. *PNAS* **91** p.4960-64 (1994)). Indeed, these experiments with wortmannin, as well as other experimental evidence, shows that PI3K activity in cells of hematopoietic lineage, particularly neutrophils, monocytes, and other types of leukocytes, is involved in many of the non-memory immune response associated with acute and chronic inflammation.



LY294002



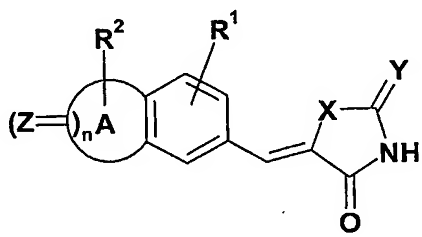
Wortmannin

Based on studies using wortmannin, there is evidence that PI3-kinase function also is required for some aspects of leukocyte signaling through G-protein coupled receptors (Thelen et al., *Proc. Natl. Acad. Sci.* USA, **91** p.4960-64 (1994)). Morever, it has been shown that wortmannin and LY294002 block neutrophil migration and superoxide release. However, in as much as these compounds do not distinguish among the various isoforms of PI3K, it remains unclear which particular PI3K isoform or isoforms are involved in these phenomena.

Azolidinone-vinyl benzene derivatives - having a mandatory benzimidazole moiety though - are described in WO 02/051409. The compounds are said to inhibit telomerase and are purportedly useful in the treatment of cancer.

Summary of the invention

The present invention relates to the use of azolidinone-vinyl fused-benzene derivatives of formula (I)



(I)

wherein A, X, Y, Z, n, R^1 and R^2 are described in details in the description hereinafter, as well as pharmaceutically acceptable salts thereof, for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation complications, graft rejection or lung injuries. Compounds of this invention are inhibitors

of Phosphato-inositides 3-kinases (PI3Ks), particularly of Phosphatoinositides 3-kinases gamma (PI3Kγ).

Description of the invention:

It has now been found that compounds of the present invention are modulators of the Phosphatoinositides 3-kinases (PI3Ks), particularly of Phosphatoinositides 3-kinase γ (PI3Kγ). When the phosphatoinositides 3-kinase (PI3K) enzyme is inhibited by the compounds of the present invention, PI3K is unable to exert its enzymatic, biological and/or pharmacological effects. The compounds of the present invention are therefore useful in the treatment and prevention of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation complications, graft rejection or lung injuries.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_6-alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-pentyl, n-hexyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"C_1-C_6-alkyl aryl" refers to C_1-C_6-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"C_1-C_6-alkyl heteroaryl" refers to C_1-C_6-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"C_2-C_6-alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl ($-CH=CH_2$), n-2-propenyl (allyl, $-CH_2CH=CH_2$) and the like.

"C_2-C_6-alkenyl aryl" refers to C_2-C_6-alkenyl groups having an aryl substituent, including 2-phenylvinyl and the like.

"C_2-C_6-alkenyl heteroaryl" refers to C_2-C_6-alkenyl groups having a heteroaryl substituent, including 2-(3-pyridinyl)vinyl and the like.

"C_2-C_6-alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

"C_2-C_6-alkynyl aryl" refers to C_2-C_6-alkynyl groups having an aryl substituent, including phenylethynyl and the like.

"C_2-C_6-alkynyl heteroaryl" refers to C_2-C_6-alkynyl groups having a heteroaryl substituent, including 2-thienylethynyl and the like.

"C_3-C_8-cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (*e.g.*, cyclohexyl) or multiple condensed rings (*e.g.*, norbornyl). Preferred cycloalkyl include cyclopentyl, cyclohexyl, norbornyl and the like.

"Heterocycloalkyl" refers to a C_3-C_8-cycloalkyl group according to the definition above, in which up to 3 carbon atoms are replaced by heteroatoms chosen from the group consisting of O, S, NR, R being defined as hydrogen or methyl. Preferred heterocycloalkyl include pyrrolidine, piperidine, piperazine, 1-methylpiperazine, morpholine, and the like.

"C_1-C_6-alkyl cycloalkyl" refers to C_1-C_6-alkyl groups having a cycloalkyl substituent, including cyclohexylmethyl, cyclopentylpropyl, and the like.

"C_1-C_6-alkyl heterocycloalkyl" refers to C_1-C_6-alkyl groups having a heterocycloalkyl substituent, including 2-(1-pyrrolidinyl)ethyl, 4-morpholinylmethyl, (1-methyl-4-piperidinyl)methyl and the like.

"Carboxy" refers to the group –C(O)OH.

"C_1-C_6-alkyl carboxy" refers to C_1-C_6-alkyl groups having an carboxy substituent, including 2-carboxyethyl and the like.

"Acyl" refers to the group –C(O)R where R includes "C_1-C_6-alkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl acyl" refers to C_1-C_6-alkyl groups having an acyl substituent, including 2-acetylethyl and the like.

"Aryl acyl" refers to aryl groups having an acyl substituent, including 2-acetylphenyl and the like.

"Heteroaryl acyl" refers to hetereoaryl groups having an acyl substituent, including 2-acetylpyridyl and the like.

"C_3-C_8-(hetero)cycloalkyl acyl" refers to 3 to 8 memebered cycloalkyl or heterocycloalkyl groups having an acyl substituent.

"Acyloxy" refers to the group –OC(O)R where R includes H, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", heterocycloalkyl"heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acyloxy" refers to C_1-C_6-alkyl groups having an acyloxy substituent, including 2-(acetyloxy)ethyl and the like.

"Alkoxy" refers to the group –O-R where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

"C_1-C_6-alkyl alkoxy" refers to C_1-C_6-alkyl groups having an alkoxy substituent, including 2-ethoxyethyl and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes H, "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl alkoxycarbonyl" refers to C_1-C_5-alkyl groups having an alkoxycarbonyl substituent, including 2-(benzyloxycarbonyl)ethyl and the like.

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen or C_1-C_6-alkyl or aryl or heteroaryl or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl".

"C_1-C_6-alkyl aminocarbonyl" refers to C_1-C_6-alkyl groups having an aminocarbonyl substituent, including 2-(dimethylaminocarbonyl)ethyl and the like.

"Acylamino" refers to the group –NRC(O)R' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl acylamino" refers to C_1-C_6-alkyl groups having an acylamino substituent, including 2-(propionylamino)ethyl and the like.

"Ureido" refers to the group –NRC(O)NR'R" where each R, R', R" is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", and where R' and R", together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ureido" refers to C_1-C_6-alkyl groups having an ureido substituent, including 2-(*N*'-methylureido)ethyl and the like.

"Carbamate" refers to the group –NRC(O)OR' where each R, R' is independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"Amino" refers to the group –NRR' where each R,R' is independently hydrogen or "C_1-C_6-alkyl" or "aryl" or "heteroaryl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", or

"cycloalkyl", or "heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl amino" refers to C_1-C_5-alkyl groups having an amino substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Ammonium" refers to a positively charged group $-N^+RR'R''$, where each R,R',R'' is independently "C_1-C_6-alkyl" or "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", or "cycloalkyl", or "heterocycloalkyl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"C_1-C_6-alkyl ammonium" refers to C_1-C_6-alkyl groups having an ammonium substituent, including 2-(1-pyrrolidinyl)ethyl and the like.

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyloxy" refers to a group $-OSO_2$-R wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an $-OSO_2$-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyloxy" refers to C_1-C_5-alkyl groups having a sulfonyloxy substituent, including 2-(methylsulfonyloxy)ethyl and the like.

"Sulfonyl" refers to group "$-SO_2$-R" wherein R is selected from H, "aryl", "heteroaryl", "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, an $-SO_2$-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl

heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonyl" refers to C_1-C_5-alkyl groups having a sulfonyl substituent, including 2-(methylsulfonyl)ethyl and the like.

"Sulfinyl" refers to a group "–S(O)-R" wherein R is selected from H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, a –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfinyl" refers to C_1-C_5-alkyl groups having a sulfinyl substituent, including 2-(methylsulfinyl)ethyl and the like.

"Sulfanyl" refers to groups –S-R where R includes H, "C_1-C_6-alkyl", "C_1-C_6-alkyl" substituted with halogens, *e.g.*, a –SO-CF_3 group, "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl". Preferred sulfanyl groups include methylsulfanyl, ethylsulfanyl, and the like.

"C_1-C_6-alkyl sulfanyl" refers to C_1-C_5-alkyl groups having a sulfanyl substituent, including 2-(ethylsulfanyl)ethyl and the like.

"Sulfonylamino" refers to a group –$NRSO_2$-R' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl"; "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl sulfonylamino" refers to C_1-C_5-alkyl groups having a sulfonylamino substituent, including 2-(ethylsulfonylamino)ethyl and the like.

"Aminosulfonyl" refers to a group $-SO_2$-NRR' where each R, R' includes independently hydrogen, "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "C_3-C_8-cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", "C_1-C_6-alkyl aryl" or "C_1-C_6-alkyl heteroaryl", "C_2-C_6-alkenyl aryl", "C_2-C_6-alkenyl heteroaryl", "C_2-C_6-alkynyl aryl", "C_2-C_6-alkynylheteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl".

"C_1-C_6-alkyl aminosulfonyl" refers to C_1-C_6-alkyl groups having an aminosulfonyl substituent, including 2-(cyclohexylaminosulfonyl)ethyl and the like.

"Substituted or unsubstituted": Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_6-alkyl", "C_2-C_6-alkenyl", "C_2-C_6-alkynyl", "cycloalkyl", "heterocycloalkyl", "C_1-C_6-alkyl aryl", "C_1-C_6-alkyl heteroaryl", "C_1-C_6-alkyl cycloalkyl", "C_1-C_6-alkyl heterocycloalkyl", "amino", "ammonium", "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "ureido", "aryl", "carbamate", "heteroaryl", "sulfinyl", "sulfonyl", "alkoxy", "sulfanyl", "halogen", "carboxy", trihalomethyl, cyano, hydroxy, mercapto, nitro, and the like. Alternatively said substitution could also comprise situations where neighbouring substituents have undergone ring closure, notably when vicinal functional substituents are involved, thus forming, *e.g.*, lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

"Pharmaceutically acceptable cationic salts or complexes" is intended to define such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium or magnesium), aluminium salts, ammonium salts and salts with organic amines such as with methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine,

morpholine, N-Me-D-glucamine, N,N'-bis(phenylmethyl)-1,2-ethanediamine, ethanolamine, diethanolamine, ethylenediamine, N-methylmorpholine, piperidine, benzathine (N,N'-dibenzylethylenediamine), choline, ethylene-diamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, thromethamine (2-amino-2-hydroxymethyl-1,3-propanediol), procaine as well as amines of formula –NR,R',R'' wherein R, R', R'' is independently hydrogen, alkyl or benzyl. Especially preferred salts are sodium and potassium salts.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-identified compounds of the present invention that retain the desired biological activity. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (*e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and poly-galacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quarternary ammonium salt of the formula –NR,R',R" $^{+}$ Z^{-}, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, cycloalkyl, heterocycloalkyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein.

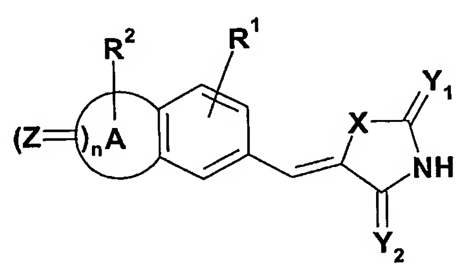
"Enantiomeric excess" (ee) refers to the products that are obtained by an asymmetric synthesis, i.e. a synthesis involving non-racemic starting materials and/or reagents or a syn-

thesis comprising at least one enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded.

General formula (I) according to the present invention also comprises its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts thereof. Preferred pharmaceutically acceptable salts of the formulae of the present invention are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and *para*-toluenesulfonate salts.

The compounds of the present invention may be obtained as E/Z isomer mixture or as essentially pure E-isomers or Z isomers. The E/Z isomerism preferably refers to the vinyl moiety linking the phenyl with the azolidinone moiety. In a specific embodiment, the compounds of formula (I) are Z-isomers.

A first aspect of the present invention consists in the use of compounds of formula (I)



(I)

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof for the preparation of a medicament for the prophylaxis and/or treatment of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet

aggregation, cancer, transplantation complications due to rejection reactions, graft rejection or lung injuries.

In a preferred embodiment, these compounds are useful for the treatment and/or prophylaxis of autoimmune diseases or inflammatory diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation such as meningitis or encephalitis.

In another preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of neurodegenerative diseases including multiple sclerosis, Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions.

In a particularly preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of cardiovascular diseases such as atherosclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

In another particularly preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of chronic obstructive pulmonary disease, anaphylactic shock fibrosis, psoriasis, allergic diseases, asthma, stroke or ischemic conditions, ischemia-reperfusion, platelets aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastisis, in particular melanoma, Karposi's sarcoma, acute and chronic bacterial and viral infections, sepsis, transplantation complications due to rejection reactions, graft rejection, glomerulo sclerosis, glomerulo nephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung or in general lung airways inflammation.

The substituents within formula (I) are defined as follows:

A is an unsubstituted or substituted 5-8 membered heterocyclic group or an unsubstituted or substituted carbocyclic group.

Said carbocyclic group may be fused with an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted cycloalkyl or an unsubstituted or substituted heterocycloalkyl.

Such heterocyclic or carbocyclic groups comprise aryl, heteroaryl, cycloalkyl and heterocycloalkyl, including phenyl, phenantrenyl, cyclopentyl, cyclohexyl, norbornyl, pyrrolidine, piperidine, piperazine, 1-methylpiperazine, morpholine, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl

Further examplary heterocyclic or carbocyclic groups A include unsubstituted or substituted dioxol, unsubstituted or substituted dioxin, unsubstituted or substituted dihydrofuran, unsubstituted or substituted (dihydro) furanyl, unsubstituted or substituted (dihydro)oxazinyl, unsubstituted or substituted oxazinoyl, unsubstituted or substituted pyridinyl, unsubstituted or substituted isooxazolyl, unsubstituted or substituted oxazolyl unsubstituted or substituted (dihydro)napthalenyl, unsubstituted or substituted pyrimidinyl, unsubstituted or substituted triazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiadiazolyl, unsubstituted or substituted oxadiazolyl.

X is S, O or NH, preferably S.

Y^1 and Y^2 are independently from each other selected from the group consisting of S, O or -NH, preferably O.

Z is S or O, preferably O.

R^1 is selected from the group comprising or consisting of H, CN, carboxy, acyl, C_1-C_6-alkoxy, halogen, hydroxy, acyloxy, an unsubstituted or substituted C_1-C_6-alkyl carboxy, an unsubstituted or substituted C_1-C_6-alkyl acyloxy, an unsubstituted or substituted C_1-C_6-alkyl alkoxy, alkoxycarbonyl, an unsubstituted or substituted C_1-C_6-alkyl alkoxycarbonyl, aminocarbonyl, an unsubstituted or substituted C_1-C_6-alkyl aminocarbonyl, acylamino, an unsubstituted or substituted C_1-C_6-alkyl acylamino, ureido, an unsubstituted or substituted C_1-C_6-alkyl ureido, amino, an unsubstituted or substituted C_1-C_6-alkyl amino, ammonium, sulfonyloxy, an unsubstituted or substituted C_1-C_6-alkyl sulfonyloxy, sulfonyl, an unsubstituted or substituted C_1-C_6-alkyl sulfonyl, sulfinyl, an unsubstituted or substituted C_1-C_6-alkyl sulfinyl, sulfanyl, an unsubstituted or substituted C_1-C_6-alkyl sulfanyl, sulfonylamino, an unsubstituted or substituted C_1-C_6-alkyl sulfonylamino or carbamate. In a specific embodiment R^1 is H.

R^2 is selected from the group comprising or consisting of H, halogen, acyl, amino, an unsubstituted or substituted C_1-C_6-alkyl, an unsubstituted or substituted C_2-C_6-alkenyl, an unsubstituted or substituted C_2-C_6-alkynyl, an unsubstituted or substituted C_1-C_6-alkyl carboxy, an unsubstituted or substituted C_1-C_6-alkyl acyl, an unsubstituted or substituted C_1-C_6-alkyl alkoxycarbonyl, an unsubstituted or substituted C_1-C_6-alkyl aminocarbonyl, an unsubstituted or substituted C_1-C_6-alkyl acyloxy, an unsubstituted or substituted C_1-C_6-alkyl acylamino, an unsubstituted or substituted C_1-C_6-alkyl ureido, an unsubstituted or substituted C_1-C_6-alkyl carbamate, an unsubstituted or substituted C_1-C_6-alkyl amino, an unsubstituted or substituted C_1-C_6-alkyl alkoxy, an unsubstituted or substituted C_1-C_6-alkyl sulfanyl, an unsubstituted or substituted C_1-C_6-alkyl sulfinyl, an unsubstituted or

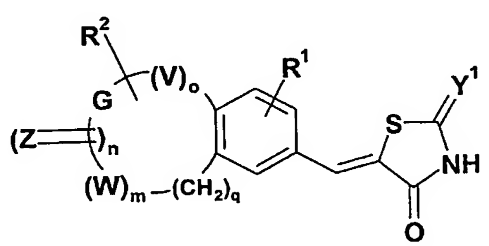
substituted C_1-C_6-alkyl sulfonyl, an unsubstituted or substituted C_1-C_6-alkyl sulfonylaminoaryl, an unsubstituted or substituted aryl, an unsubstituted or substituted C_3-C_8-cycloalkyl or heterocycloalkyl, an unsubstituted or substituted C_1-C_6-alkyl aryl, an unsubstituted or substituted C_2-C_6-alkenyl-aryl, an unsubstituted or substituted C_2-C_6-alkynyl aryl, carboxy, cyano, hydroxy, C_1-C_6-alkoxy, nitro, acylamino, ureido, sulfonylamino, sulfanyl, or sulfonyl.

n is an integer 0, 1 or 2, preferably n is 0 or 1. Most preferred is n = 0.

According to a specific embodiment of the invention, R^1 and R^2 are both H.

In a further specific embodiment according to the invention, X is S, Y^1 and Y^2 are both O, R^1 and R^2 are as above defined and n is 0.

A further particularly preferred aspect of the present invention is related to the use of thiazolidinedione-vinyl fused-benzene derivatives of formula (Ia), (Ib), (Ic) and (Id) for the preparation of a medicament for the prophylaxis and/or treatment of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation complications due to rejection reactions, graft rejection or lung injuries :



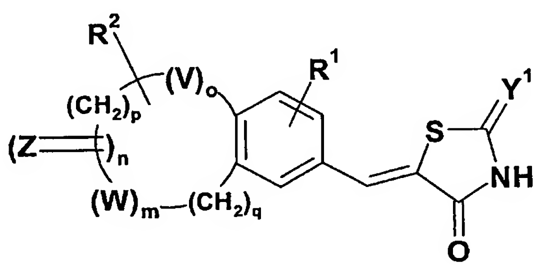
(Ia)

R^1, R^2, Y^1, Z and n in formula (Ia) are as above-defined.

G in formula (Ia) is an unsubstituted or substituted C_1-C_5 alkylene (e.g. methylene, ethylene, propylene etc.) or an unsubstituted or substituted C_1-C_5 alkenylene group (e.g. a methine (-CH=), a -CH=CH- group, a propenylene group, etc.).

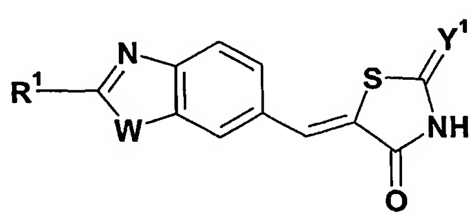
W and V in formula (Ia) are each independently from each other selected from O, S, $-NR^3$ wherein R^3 is H or an unsubstituted or substituted C_1-C_6 alkyl group, m and o are each independently from each other 0 or 1; o is an integer from 1 to 4 and q is an integer from 0 to 4.

Even more preferred compounds of formula (Ia) is where G is an C_1-C_4 alkylene, thus giving compounds of formula (Ib) (i.e. p = 1, 2, 3 or 4, preferably 1 or 2).



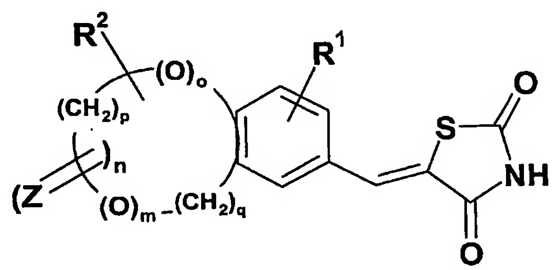
(Ib)

A specific sub-group of formula (Ib) are compounds having the formula (Ic), whereby W, R^1, Y^1 are as above defined; specifically R^1 may be an unsubstituted or substituted C_1-C_4 alkyl group or an unsubstituted or substituted C_1-C_5 alkenyl group, carboxy, cyano, C_1-C_4-alkoxy, nitro, acylamino, ureido.



(Ic)

Still a further specific sub-group of formula (Ia) are compounds, wherein V, W and Y^1 are all O, thus providing compounds of formula (Id).



(Id)

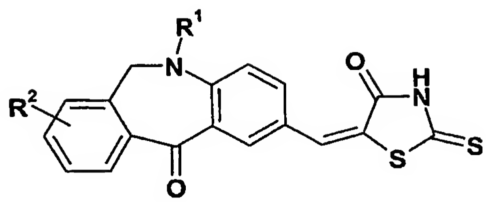
In a preferred embodiment of formulae (Ia), (Ib) or (Id), n is 0, m is 1, p is 1 or 2, o is 0, q is 1, and R^1 and R^2 are as above-defined.

In a further specific embodiment of formulae (Ia), (Ib) or (Id), m is 1, n is 0, p is 1 or 2, q is 0, o is 1 while R^1 and R^2 are as above-defined, more particularly R^1 is halogen or a hydrogen atom.

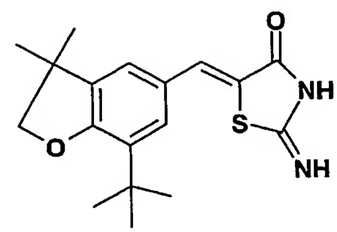
In another specific embodiment of formula (Ia), (Ib) or (Id), p is 1 or 2, q is 0, m is 0, n is 1 and R^1 and R^2 are as above-defined.

The compounds of the present invention are suitable for the modulation, notably the inhibition of the activity of phosphatoinositides 3-kinases (PI3K), particularly phosphatoinositides 3-kinase (PI3Kγ). It is therefore believed that the compounds of the present invention are also particularly useful for the treatment and/or prevention of disorders which are mediated by PI3Ks, particularly PI3Kγ. Said treatment involves the modulation – notably the inhibition or the down regulation – of the phosphatoinositides 3-kinases.

The following compounds are not included by formula (I) :



(TE)



(JA)

R^1 is a lower alkyl or aralkyl and R^2 is H or a halogen. The compounds TE are disclosed in JP 55 045648 as intermediate compounds without any biological activity, while JA is mentioned in the *Journal of Medicinal Chemistry* (1998), 41(18), 3515-3529 as being inactive in a paw swelling assay.

Compounds of the present invention include in particular those of the group consisting of:

5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione

5-(1,3-benzodioxol-5-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one

5-(2,3-dihydro-1,4-benzodioxin-6-ylmethylene)-1,3-thiazolidine-2,4-dione

5-(2,3-dihydro-1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione

5-[(7-methoxy-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione

5-[(9,10-dioxo-9,10-dihydroanthracen-2-yl)methylene]-1,3-thiazolidine-2,4-dione

(5-[(2,2-difluoro-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione

(5Z)-5-(1,3-dihydro-2-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione

5-(1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione

5-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-(1,3-benzodioxol-5-ylmethylene)-2-imino-1,3-thiazolidin-4-one

5-Quinolin-6-ylmethylene-thiazolidine-2,4-dione

5-Quinolin-6-ylmethylene-2-thioxo-thiazolidin-4-one

2-Imino-5-quinolin-6-ylmethylene-thiazolidin-4-one

5-(3-Methyl-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione

5-(4-Phenyl-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione

5-(4-Dimethylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione

5-[(4-aminoquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-[(4-piperidin-1-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-[(4-morpholin-4-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-{[4-(benzylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-{[4-(diethylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-({4-[(pyridin-2-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({4-[(pyridin-3-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione

ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-3-carboxylate

ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-4-carboxylate

tert-butyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}-L-prolinate

5-{[4-(4-methylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-{[4-(4-pyrimidin-2-ylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-({4-[4-(4-fluorophenyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-{[4-(4-benzylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-({4-[4-(2-phenylethyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-{[4-(4-methylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-{[4-(4-hydroxypiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione

1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-4-carboxylic acid

1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-3-carboxylic acid

1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-pyrrolidine-2-carboxylic acid

5-(4-Methylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione

5-(4-Methoxy-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione

2-Imino-5-(4-methylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one

2-Imino-5-(4-piperidine-quinazolin-6-ylmethylene)-thiazolidin-4-one

2-Imino-5-(4-dimethylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one

5-(2-Methyl-2H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione

5-(3-Methyl-3H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione

5-(3-Ethyl-3H-benzoimidazol-5-ylmethylene)-thiazolidine-2,4-dione

5-{[1-(4-phenylbutyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-[(1-prop-2-yn-1-yl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-[(1-{2-[4-(trifluoromethyl)phenyl]ethyl}-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-({1-[2-(4-hydroxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

methyl 4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylate

5-({1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({1-[2-(3,4-dimethoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({1-[2-(4-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({1-[4-(trifluoromethyl)benzyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylic acid

5-[(1-isobutyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-({1-[2-(1,3-benzodioxol-4-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({1-[2-(2-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione

5-{[1-(3,3-diphenylpropyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-{[1-(2-methoxybenzyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-{[1-(3-furylmethyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione

5-[(1-propyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione

5-Quinoxalin-6-ylmethylene-thiazolidine-2,4-dione

5-Quinoxalin-6-ylmethylene-2-thioxo-thiazolidin-4-one

2-Imino-5-quinoxalin-6-ylmethylene-thiazolidin-4-one

5-Benzothiazol-6-ylmethylene-thiazolidine-2,4-dione

5-(3-Methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

5-(2-Bromo-3-methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

5-(3-bromo-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid ethyl ester

3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid

5-[3-(3-Oxo-3-piperidin-1-yl-propenyl)-benzofuran-5-ylmethylene]-thiazoli-dine-2,4-dione

Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)prolinate

Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-D-prolinate

(5-({3-[(3-oxo-3-pyrrolidin-1-ylprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({3-[3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

Methyl 1-(3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-L-prolinate

N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-methylacrylamide

3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-ethyl-N-(2-hydroxyethyl)acrylamide

N-cyclobutyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide

5-({3-[3-azetidin-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({3-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

5-({3-[3-azepan-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-piperidin-1-ylacrylamide

3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-(pyridin-3-ylmethyl)acrylamide

N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide

5-({3-[3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

N-cycloheptyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide

5-({3-[3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione

N-cyclopentyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide

3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid ethyl ester

3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid

5-[3-(3-Oxo-3-piperidin-1-yl-propyl)-benzofuran-5-ylmethylene]-thiazol-idine-2,4-dione

6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

5-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione

5-(4-Benzoyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione

5-(4-Acetyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione

6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-acetic acid methyl ester

N-Benzyl-2-[6-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetamide

5-(4-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazoli-dine-2,4-dione

5-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thia-zolidine-2,4-dione

5-(2-Chloro-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

5-(3-Amino-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione

5-(3-Phenylethynyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

5-Benzo[1,2,5]thiadiazol-5-ylmethylene-thiazolidine-2,4-dione

5-Benzo[1,2,5]oxadiazol-5-ylmethylene-thiazolidine-2,4-dione

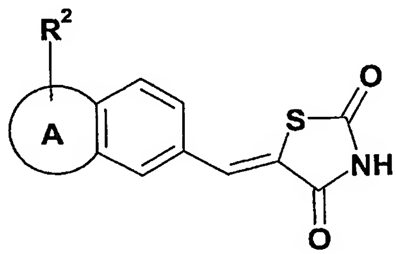
5-(2-Methyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

5-(2-Carboxymethyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

5-(3-Bromo-2-fluoro-2,3-dihydro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

5-(2-Fluoro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

A further aspect of the invention consists in novel thiazolidindione-vinyl fused-benzene derivatives of formula (II-a)



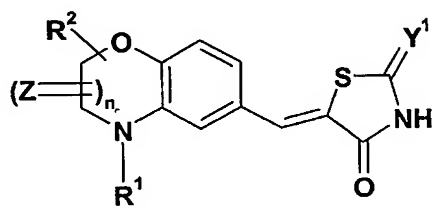
(II-a)

A is selected from the group consisting of unsubstituted or substituted dioxol, unsubstituted or substituted dioxin, unsubstituted or substituted dihydrofuran, unsubstituted or substituted (dihydro) furanyl, unsubstituted or substituted (dihydro)oxazinyl, unsubstituted or substituted oxazinoyl, unsubstituted or substituted pyridinyl, unsubstituted or substituted isooxazolyl, unsubstituted or substituted oxazolyl unsubstituted or substituted (dihydro)napthalenyl, unsubstituted or substituted pyrimidinyl, unsubstituted or substituted triazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted pyrazinyl, unsubstituted or substituted thiazolyl, unsubstituted or substituted thiadiazolyl, unsubstituted or substituted oxadiazolyl.

R^2 is selected from the group comprising or consisting of H, halogen, acyl, amino, unsubstituted or substituted C_1-C_6-alkyl, unsubstituted or substituted C_2-C_6-alkenyl, unsubstituted or substituted C_2-C_6-alkynyl, unsubstituted or substituted C_1-C_6-alkyl carboxy, unsubstituted or substituted C_1-C_6-alkyl acyl, unsubstituted or substituted C_1-C_6-alkyl alkoxycarbonyl, unsubstituted or substituted C_1-C_6-alkyl aminocarbonyl, unsubstituted or substituted C_1-C_6-alkyl acyloxy, unsubstituted or substituted C_1-C_6-alkyl

acylamino, unsubstituted or substituted C_1-C_6-alkyl ureido, unsubstituted or substituted C_1-C_6-alkyl carbamate, unsubstituted or substituted C_1-C_6-alkyl amino, unsubstituted or substituted C_1-C_6-alkyl alkoxy, unsubstituted or substituted C_1-C_6-alkyl sulfanyl, unsubstituted or substituted C_1-C_6-alkyl sulfinyl, unsubstituted or substituted C_1-C_6-alkyl sulfonyl, unsubstituted or substituted C_1-C_6-alkyl sulfonylaminoaryl, an unsubstituted or substituted aryl, unsubstituted or substituted C_3-C_8-cycloalkyl or heterocycloalkyl, unsubstituted or substituted C_1-C_6-alkyl aryl, unsubstituted or substituted C_2-C_6-alkenyl-aryl, unsubstituted or substituted C_2-C_6-alkynyl aryl, carboxy, cyano, hydroxy, C_1-C_6-alkoxy, nitro, acylamino, ureido, sulfonylamino, sulfanyl, or sulfonyl.

More specific novel thiazolidinone-vinyl fused-benzene derivatives of formula (II)



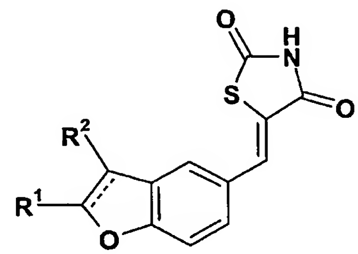
(II)

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein Y^1, Z, R^1, R^2 are as above defined and n is 0 or 1.

In a specific embodiment R^1 is an unsubstituted or substituted C_1-C_6-alkyl, an unsubstituted or substituted C_1-C_6-alkyl aryl, an unsubstituted or substituted aryl, an unsubstituted or substituted C_3-C_8-cycloalkyl or -heterocycloalkyl, an unsubstituted or substituted C_1-C_6-alkyl aryl, an unsubstituted or substituted C_2-C_6-alkenyl-aryl, an unsubstituted or substituted C_2-C_6-alkynyl aryl.

In another preferred embodiment according to the present invention Y^1 is O.

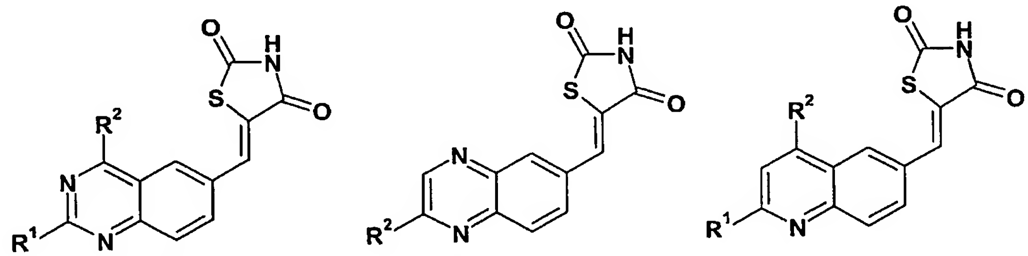
Still another aspect of the invention consists in novel thiazolidinone-vinyl fused-benzene derivatives of formula (III)



(III)

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein R^1 and R^2 are as above defined (the dotted line represents the optional presence of a double bond).

Still a further embodiment comprises compounds of formulae (IV), (V) and (VI) :



(IV) (V) (VI)

R^1 is selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, acyl, alkoxy cabonyl, while R^2 is as above defined. In a specific embodiment R^2 is an amino moiety.

A further aspect of the present invention is the use of the novel compounds of formulae (II), (II-a), (III), (IV), (V) or (VI) as medicament.

Another further aspect of the invention is a pharmaceutical composition containing at least one thiazolidinone-vinyl fused-benzene derivative according to formulae (II), (III), (IV), (V) or (VI) and a pharmaceutically acceptable carrier, diluent or excipient thereof.

Still a further aspect of the invention is the use of compounds according to formula (II), (III), (IV), (V) or (VI) for the preparation of a medicament for the prophylaxis and/or treatment of diseases mediated by a PI3 Kinase, particularly PI3 Kinase γ.

Specific diseases are the ones selected in the group comprising or consisting of autoimmune disorders and/or inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, bacterial or viral infections, kidney diseases, platelet aggregation, cancer, transplantation complications due to rejection reactions, graft rejection or lung injuries.

In a preferred embodiment, said compounds are useful for the treatment and/or prophylaxis of autoimmune diseases or inflammatory diseases such as multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, lung inflammation, thrombosis or brain infection/inflammation such as meningitis or encephalitis.

In another preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of neurodegenerative diseases including multiple sclerosis, Alzheimer's disease, Huntington's disease, CNS trauma, stroke or ischemic conditions.

In a particularly preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of cardiovascular diseases such as atherosclerosis, heart hypertrophy, cardiac myocyte dysfunction, elevated blood pressure or vasoconstriction.

In another particularly preferred embodiment according to the invention, these compounds are useful for the treatment and/or prophylaxis of chronic obstructive pulmonary disease,

anaphylactic shock fibrosis, psoriasis, allergic diseases, asthma, stroke or ischemic conditions, ischemia-reperfusion, platelets aggregation/activation, skeletal muscle atrophy/hypertrophy, leukocyte recruitment in cancer tissue, angiogenesis, invasion metastisis, in particular melanoma, Karposi's sarcoma, acute and chronic bacterial and viral infections, sepsis, transplantation complications due to rejection reactions, graft rejection, glomerulo sclerosis, glomerulo nephritis, progressive renal fibrosis, endothelial and epithelial injuries in the lung or in general lung airways inflammation.

According to the present invention, compounds of formula (II), (II-a), (III) (IV), (V) or (VI) are suitable to modulate, particularly to inhibit, PI3 kinase activity and more particularly PI3Kγ activity.

Still a further object of the present invention is a process for preparing azolidinone-vinyl fused-benzene derivatives according to formula (I), (Ia), (Ib), (Ic) or (Id) but also thiazolidinone-vinyl fused-benzene derivatives of formulae (II), (II-a), (III), (IV), (V) or (VI).

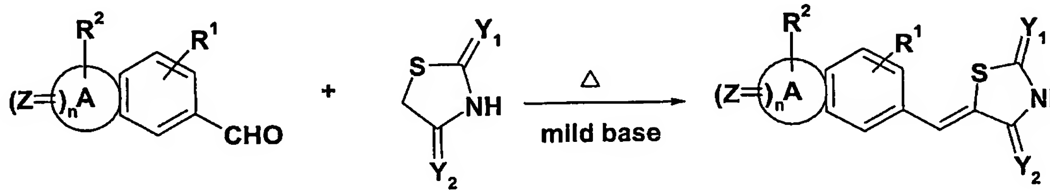
The azolidinone-vinyl fused-benzene derivatives exemplified in this invention may be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimisation procedures.

In the process illustrated in the following schemes R^1, R^2, G, V, W, Y^1, Y^2, Z, m, n, o, p and q are each as above-defined in the description.

Generally, the azolidinone-vinyl fused-benzene derivatives according to the general formula (I) could be obtained by several synthetic approaches, using both solution-phase

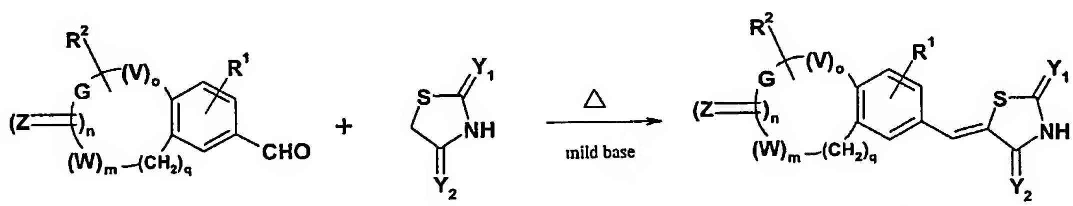
and solid-phase chemistry protocols (Brummond et.al., *J.O.C.*, **64**, 1723-1726 (1999)), either by conventional methods or by microwave-assisted techniques.

Scheme 1



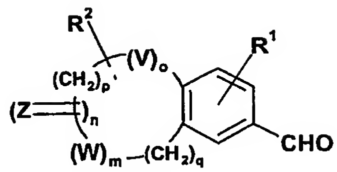
P1 P (I)

Scheme 2

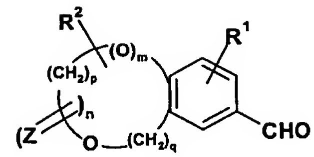


P1a P3 (Ia)

In a first step, approximately equimolar amounts of the aldehyde reactant P1 (P1a) and compound 2 (in particular thiazolidinedione or rhodanin P3) are heated in the presence of a preferably mild base to provide the corresponding olefin of formula (Ia). In the first step, P1a may be replaced by precursors P1b and P1c in order to obtain the final compounds (Ib) and (Ic) respectively as above described in the description.



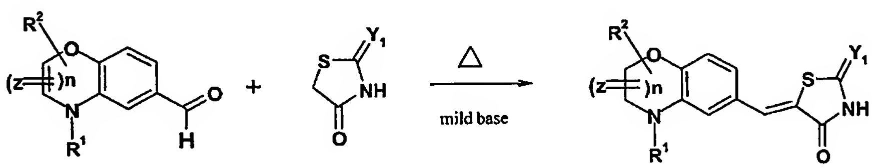
P1b



P1c

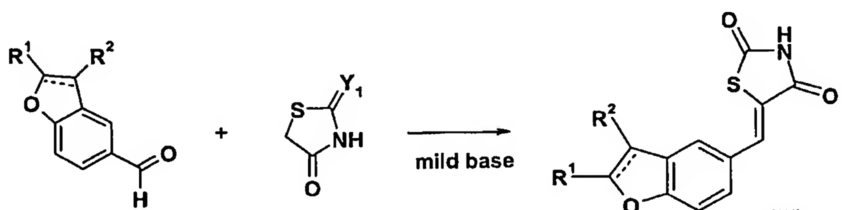
Particularly preferred process according to the invention are illustrated by the following schemes 3 and 4 in which compounds of formula (II) and (III) respectively, may be obtained using the same reaction as above-mentioned.

Scheme 3



P2 P3' (II)

Scheme 4



(III)

While this step may be carried out in the absence of a solvent at a temperature, which is sufficiently high to cause at least partial melting of the reaction mixture, it is preferably carried out in the presence of a inert solvent. A preferred temperature range is from about 100°C to 250°C, and especially preferred is a temperature of from about 120°C to 200°C. Examples of such solvents for the above reaction include solvents like dimethoxymethane, xylene, toluene, o-dichlorobenzene etc. Examples of suitable mild bases for the above reaction are alkali metal and alkaline earth salts of week acids such as the (C_1-C_{12})-alkyl

carboxylic acids and benzoic acid, alkali metal and alkaline earth carbonates and bicarbonates such as calcium carbonate, magnesium carbonate, potassium bicarbonate and secondary amines such as piperidine, morpholine as well as tertiary amines such as pyridine, triethylamine, diisopropylethylamine, N-methylmorpholine, N-ethylpiperidine, N-methylpiperidine and the like. Especially preferred mild bases are sodium acetate or piperidine for reasons of economy and efficiency.

In a typical such reaction (Tietze et.al., in "The Knoevenagel reaction", p.341 ff., Pergamon Press, Oxford 1991, Eds.: Trost B.M., Fleming I.) the aldehyde starting material P1a and the other starting compound (e.g. thiazolidinedione) P3 are combined in approximately equimolar amounts with 0.5 to one equivalent of piperidine in dimethoxymethane or similar solvent and heated between 120 and 200°C at which the reaction is substantially complete in from about 15 minutes to 3 hours. The desired olefin of formula (Ia) is then isolated by filtration, in case it precipitated out of the reaction mixture upon cooling, or for example, by mixing with water and subsequent filtration, to obtain the crude product, which is purified, if desired, e.g. by crystallization or by standard chromatographic methods.

Alternatively compounds of formula (Ia) may be obtained typically by mixing equimolar amounts of thiazolidinedione P3 with aldheyde P1a and molar excess, preferably a 2-4 fold excess, of anhydrous sodium acetate and the mixture is heated at a temperature high enough to effect melting, at which temperature the reaction is mainly complete in from 5 to 60 minutes.

Preferably the above reaction is carried out in acidic media such as acetic acid in the presence of sodium acetate or beta-alanine.

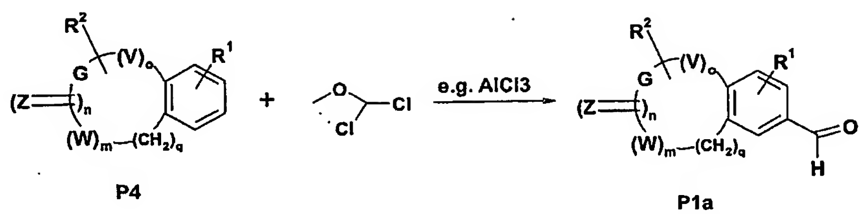
Above described reactions may be carried out alternatively under microwave conditions as heating source. Typically the aldehyde starting material P1a and thiazolidinedione P3 are combined in approximately equimolar amounts with 0.5 to one equivalent of piperidine in

dimethoxymethane or similar solvent and heated between 140°C and 240°C at which the reaction is substantially complete in from 3 to 10 minutes.

The pharmaceutically acceptable cationic salts of compounds of the present invention are readily prepared by reacting the acid forms with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hxdroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium hydroxide, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, ethylenediamine, meglumine, benethamine, diethylamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In some cases, salts can be prepared by mixing a solution of the acid with a solution of the cation (sodium ethylhexanoate, magnesium oleate), employing a solvent in which the desired cationic salt precipitates, or can be otherwise isolated by concentration and addition of a non-solvent.

2,4-Azolidinone derivatives P3 are commercially available from various sources. The aldehydes of formula P1a are prepared by a variety of well known methods, for example starting from the corresponding carboxylic acid alkyl ester or carboxylic acid by oxido-reduction, using standard techniques to reduce carboxylic acid alkyl ester or carboxylic acid to benzylic alcohols with lithium aluminium hydride, diisopropylaluminum etc. and ultimately re-oxidize the corresponding benzylic alcohol to the corresponding aldehyde by mild oxidation with reagents such as manganese dioxide, chromic acid, Dess-Martin reagent or Swern oxidation, or under conditions known to produce aldehydes from primary alcohols. An alternative way may be the direct reduction of the corresponding carboxylic acid alkyl ester or carboxylic acid to the corresponding aldehyde, using DIBAL at low temperature or any other techniques known in the field.

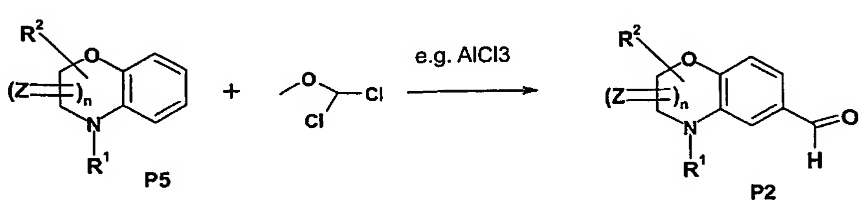
Scheme 5



An alternative way to prepare the appropriate aldehydes is the selective reduction of a nitrile moiety to the corresponding aldehyde using known methods like e.g. DIBAL etc. Another way to access aldehydes of formula P1a is the selective reduction of the corresponding acyl chloride using e.g. Lithiumaluminium-tri-tert-butoxyhydride (Cha J.S., Brown H.C., *J.O.C* 1993, **58**, p.4732-34). Another alternative way to produce the appropriate aldehydes is the reaction of the corresponding benzene derivative in a Friedl-Crafts type of reaction wherein the substrate P4 as shown in the above scheme 5 is reacted with 1,1-dichloromethylmethyl ether in the presence of a Lewis acid such as titanium tetrachloride or aluminium trichloride or any corresponding Lewis acids suitable for such type of reaction.

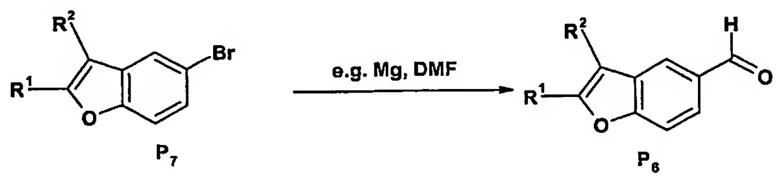
Acccording to a more particularly preferred process of the invention, as described in the literature (Petrov O.I., Kalcheva V.B., Antonova A.T., *Collect. Czech. Chem. Commun*, **62,** p.494-7 (1997)) and illustrated by Scheme 6 hereinafter, reactant P2 may be obtained starting from P5 by reacting with 1,1-dichloromethylmethyl ether as above-described.

Scheme 6



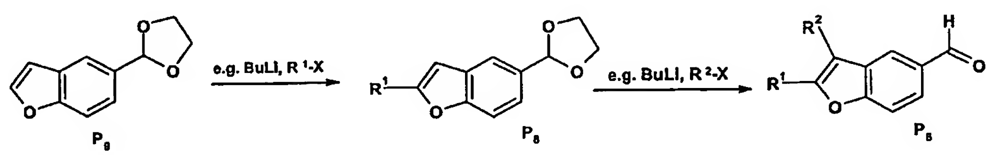
Acccording to another more particularly preferred process of the invention, as illustrated by Scheme 7 hereinafter, reactant P6 may be obtained starting from P7 by reacting with DMF and the presence of magnesium or *n*-butyl-lithium or any other method known to the person skilled in the art.

Scheme 7



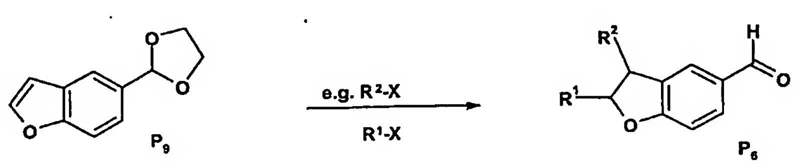
Acccording to another more particularly preferred process of the invention, as illustrated by Scheme 8 hereinafter, reactant P6 may be obtained starting from P9 by reacting n-butyllithium or LDA in the presence of an appropriate electrophile R^1-X, or any other method known to the person skilled in the art. This method may be repeated for P8 in order to obtain P6 accordingly.

Scheme 8



Similarily, saturated precursors P6 may be obtained in a one-pot reaction using P9 and appropriate electrophiles R^1-X and R^2-X as set out in Scheme 9.

Scheme 9



If the above set out general synthetic methods are not applicable to obtain compounds according to formula (I) and/or to necessary intermediates for the synthesis of compounds of formula (I), suitable methods of preparation known by a person skilled in the art should be used. In general, the synthesis pathways for any individual compound of formula (I) will depend on the specific substitutents of each molecule and upon the ready availability of intermediates necessary; again such factors being appreciated by those of ordinary skill in the art.

For all the protection and deprotection methods, see Philip J. Kocienski, in "*Protecting Groups*", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "*Protective Groups in Organic Synthesis*", Wiley Interscience, 3rd Edition 1999.

Compounds of this invention can be isolated in association with solvent molecules by crys-tallization from evaporation of an appropriate solvent. The pharmaceutically acceptable acid addition salts of the compounds of of the present invention which contain a basic center, may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solu-tion of compound of the present invention with a suitable base. Both types of salts may be formed or interconverted using ion-exchange resin techniques.

When employed as pharmaceuticals, azolidinedione-vinyl fused-benzene derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of the present invention a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

Pharmaceutical compositions containing azolidinedione-vinyl fused-benzene derivatives of this invention can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the present invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes

of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the thiazolidinedione-vinyl fused-benzene derivative is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the thiazolidinedione-vinyl fused-benzene derivatives of formula (I) in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 5 of *Remington's Pharmaceutical Sciences*, 20th Edition, 2000, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention. The following abbreviations are hereinafter used in the accompanying examples: min (minute), hr (hour), g (gram), mmol (millimole), m.p. (melting point), eq (equivalents), ml (milliliter), µl (microliters), ACN (acetonitrile), Boc (butoxycarbonyl), Cbz (carboxybenzyl), $CDCl_3$ (deuterated chloroform), cHex (cyclohexane), dba (dibenzylideneacetone), DCM (dichloromethane), DEAD (diethylazodicarboxylate, DIC (diisopropylcarbodiimide), DIEA (diisopropylethylamine), DMAP (4-dimethylaminopyridine), DME (dimethoxyethane), DMF (dimethylformamide), DMSO (dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), EtOAc (ethylacetate), Et_2O (diethylether), Fmoc (9-fluorenylmethoxy-carbonyl), HOBt (1-hydroxybenzotriazole), K_2CO_3 (potassium carbonate), $MgSO_4$ (magnesium sulfate), MsCl (methylsulfonylchloride), MTBE (*tert*-butylmethylether), NaH (sodium hydride), $NaHCO_3$ (sodium bicarbonate), nBuLi (n-butyllithium), PCC (pyridinium chlorochromate), PE (petroleum ether), QCl (tetrabutylammonium chloride), rt (room temperature), TBTU (*O*-benzotriazolyl-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate), TEA (triethylamine), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TMOF (trimethylorthoformate), TMAD (*N,N,N',N'*-tetramethylazodicarboxamide), TosCl (toluenesulfonylchloride).

<u>Examples:</u>

The following list of compounds were synthesized according to the below mentioned methods:

Example	Name
1	5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione
2	5-(1,3-benzodioxol-5-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one
3	5-(2,3-dihydro-1,4-benzodioxin-6-ylmethylene)-1,3-thiazolidine-2,4-dione
4	5-(2,3-dihydro-1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione

5	5-[(7-methoxy-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione
6	5-[(9,10-dioxo-9,10-dihydroanthracen-2-yl)methylene]-1,3-thiazolidine-2,4-dione
7	(5-[(2,2-difluoro-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione
8	(5Z)-5-(1,3-dihydro-2-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione
9	5-(1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione
10	5-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methylene]-1,3-thiazolidine-2,4-dione
11	5-(1,3-benzodioxol-5-ylmethylene)-2-imino-1,3-thiazolidin-4-one
12	5-Quinolin-6-ylmethylene-thiazolidine-2,4-dione
13	5-Quinolin-6-ylmethylene-2-thioxo-thiazolidin-4-one
14	2-Imino-5-quinolin-6-ylmethylene-thiazolidin-4-one
15	5-(3-Methyl-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione
16	5-(4-Phenyl-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione
17	5-(4-Dimethylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione
18	5-[(4-aminoquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione
19	5-[(4-piperidin-1-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione
20	5-[(4-morpholin-4-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione
21	5-{[4-(benzylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
22	5-{[4-(diethylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
23	5-({4-[(pyridin-2-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione
24	5-({4-[(pyridin-3-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione
25	ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-3-carboxylate
26	ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-4-carboxylate

27	tert-butyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}-L-prolinate
28	5-{[4-(4-methylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
29	5-{[4-(4-pyrimidin-2-ylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
30	5-({4-[4-(4-fluorophenyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione
31	5-{[4-(4-benzylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
32	5-({4-[4-(2-phenylethyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione
33	5-{[4-(4-methylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
34	5-{[4-(4-hydroxypiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione
35	1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-4-carboxylic acid
36	1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-3-carboxylic acid
37	1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-pyrrolidine-2-carboxylic acid
38	5-(4-Methylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione
39	5-(4-Methoxy-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione
40	2-Imino-5-(4-methylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one
41	2-Imino-5-(4-piperidine-quinazolin-6-ylmethylene)-thiazolidin-4-one
42	2-Imino-5-(4-dimethylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one
43	5-(2-Methyl-2H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione
44	5-(3-Methyl-3H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione
45	5-(3-Ethyl-3H-benzoimidazol-5-ylmethylene)-thiazolidine-2,4-dione
46	5-{[1-(4-phenylbutyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione

47	5-[(1-prop-2-yn-1-yl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione
48	5-[(1-{2-[4-(trifluoromethyl)phenyl]ethyl}-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione
49	5-({1-[2-(4-hydroxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
50	methyl 4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylate
51	5-({1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
52	5-({1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
53	5-({1-[2-(3,4-dimethoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
54	5-({1-[2-(4-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
55	5-({1-[4-(trifluoromethyl)benzyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
56	4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylic acid
57	5-[(1-isobutyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione
58	5-({1-[2-(1,3-benzodioxol-4-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
59	5-({1-[2-(2-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione
60	5-{[1-(3,3-diphenylpropyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione
61	5-{[1-(2-methoxybenzyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione
62	5-{[1-(3-furylmethyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione
63	5-[(1-propyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione
64	5-Quinoxalin-6-ylmethylene-thiazolidine-2,4-dione
65	5-Quinoxalin-6-ylmethylene-2-thioxo-thiazolidin-4-one
66	2-Imino-5-quinoxalin-6-ylmethylene-thiazolidin-4-one

67	5-Benzothiazol-6-ylmethylene-thiazolidine-2,4-dione
68	5-(3-Methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione
69	5-(2-Bromo-3-methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione
70	5-(3-bromo-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione
71	3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid ethyl ester
72	3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid
73	5-[3-(3-Oxo-3-piperidin-1-yl-propenyl)-benzofuran-5-ylmethylene]-thiazoli-dine-2,4-dione
74	Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)prolinate
75	Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-D-prolinate
76	(5-({3-[(3-oxo-3-pyrrolidin-1-ylprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
77	5-({3-[3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
78	Methyl 1-(3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-L-prolinate
79	N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-methylacrylamide
80	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-ethyl-N-(2-hydroxyethyl)acrylamide
81	N-cyclobutyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide
82	5-({3-[3-azetidin-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
83	5-({3-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
84	5-({3-[3-azepan-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
85	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-piperidin-1-ylacrylamide

86	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-(pyridin-3-ylmethyl)acrylamide
87	N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide
88	5-({3-[3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
89	N-cycloheptyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide
90	5-({3-[3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione
91	N-cyclopentyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide
92	3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid ethyl ester
93	3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid
94	5-[3-(3-Oxo-3-piperidin-1-yl-propyl)-benzofuran-5-ylmethylene]-thiazol-idine-2,4-dione
95	6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester
96	5-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione
97	5-(4-Benzoyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione
98	5-(4-Acetyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione
99	6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester
100	[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-acetic acid methyl ester
101	N-Benzyl-2-[6-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetamide
102	5-(4-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione
103	5-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione

104 5-(2-Chloro-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

105 5-(3-Amino-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione

106 5-(3-Phenylethynyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione

107 5-Benzo[1,2,5]thiadiazol-5-ylmethylene-thiazolidine-2,4-ione

108 5-Benzo[1,2,5]oxadiazol-5-ylmethylene-thiazolidine-2,4-ione

109 5-(2-Methyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

110 5-(2-Carboxymethyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

111 5-(3-Bromo-2-fluoro-2,3-dihydro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

112 5-(2-Fluoro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

The following intermediate aldehydes are commercially available: 2,2-Difluoro-1,3-benzodioxole-5-carboxaldehyde, 1,3-Benzodioxole-5-carboxaldehyde, 1,4-Benzodioxan-6-carboxaldehyde, 9,10-Dioxo-9,10-dihydro-anthracene-2-carbaldehyde, 2,3-Dihydro-benzo[b]furan-5-carboxaldehyde, 3-Methoxy-4,5-methylenedioxybenzaldehyde.

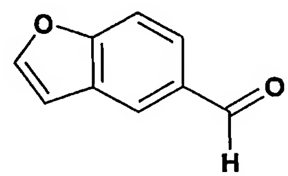
Thiazolidinedione and Rhodanine are commercially available. Intermediate aldehydes were synthesized according to the protocols as mentioned below.

The HPLC, NMR and MS data provided in the examples described below were obtained as followed: HPLC: column Waters Symmetry C8 50 x 4.6 mm, Conditions: $MeCN/H_2O$, 5 to 100% (8 min), max plot 230-400 nm; Mass spectra: PE-SCIEX API 150 EX (APCI and ESI), LC/MS spectra: Waters ZMD (ES); ^{1}H-NMR: Bruker DPX-300MHz.

The purifications were obtained as followed: Preparative HPLC Waters Prep LC 4000 System equipped with columns Prep Nova-Pak®HR C186 µm 60Å, 40x30mm (up to

100mg) or 40x300 mm (up to 1g). All the purifications were performed with a gradient of MeCN/H_2O 0.09% TFA.

Intermediate 1: Preparation of 5-formyl-1-benzofuran



Step I Ethyl-2-formyl-4-bromophenoxy acetate:

A mixture of 5-bromosalicylaldehyde (50g, 0.248mol), ethylbromoacetate (42g, 0.248mol) and K_2CO_3 (68g, 0.49mol) in dry DMF (200mL) was stirred at RT for 12h. The reaction mixture was filtered and filtrate diluted with water. The mixture was extracted with diethylether (4x200mL), washed with brine and concentrated to give crude ethyl-2-formyl-4-bromophenoxy acetate (64g, 90%) as a solid.

Step II: 4-Bromo-2-formylphenoxy acetic acid:

A mixture of ethyl-2-formyl-4-bromophenoxy acetate (60g, 0.209mol), LiOH (7.5g, 0.31mol), THF (250mL) and water (100mL) was stirred at RT for 24h. The reaction mixture was concentrated under reduce pressure and residue acidified with 1.5N HCl to pH=2. The solid precipitate obtained was filtered and dried to give 4-bromo-2-formylphenoxy acetic acid (50g, 94%).

Step III: 5-Bromo-1-benzofuran:

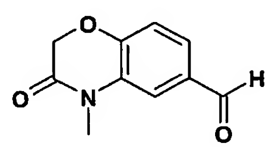
To a mixture of 2-formyl-4-bromophenoxy acetic acid (50g, 0.192mol), sodium acetate (100g, 1.21mol) in acetic acid (250mL) at 100°C was added acetic anhydride (100mL) portions during a period of 3h. The reaction mixture was then refluxed for 20h. The solvent was removed by distillation and residue diluted with 3N HCl (500mL) and refluxed for 2h. The reaction mixture was then concentrated under vacuum and product extracted with pet.

ether (3x200mL). The organic layer was washed with 10% $NaHCO_3$ solution and evaporated to give 5-bromo-1-benzofuran (15g, 40%) as a pale yellow liquid.

Step IV: 5-Formyl-1-benzofuran (P1a in scheme 2 for example 9):

A mixture of 5-bromo-1-benzofuran (0.5g), Mg (0.92g, 0.038mol), I_2 (1 crystal) in dry THF (2.5mL) under N_2 atmosphere was refluxed for 30min. To this was added a solution of 5-bromo-1-benzofuran (4.5g) in 25mL of dry THF) as soon as the I_2 color disappear and refluxed for another 2h. The reaction mixture was then cooled to –40°C and added dry DMF (3.6g) drop-wise and slowly warmed to RT for a period of 12h. The reaction mixture was then cooled to 0°C and acidified with 3N HCl to pH=2 and stirred for 30min. The reaction mixture was then diluted with water (500mL), extracted with ethylacetate (2x200mL), washed with brine and dried. The solvent was removed under vacuum and purified by column chromatography over silica gel (pet. ether/CH_2Cl_2) to give 5-formyl-1-benzofuran (2g, 54%) as a liquid. LC-MS: M/Z ESI: 1.47 min, 147.34 (M+1).

Intermediate 2: Preparation of 4-Methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde



Step I: 2-(N-methylamino)-phenol:

1g of benzoxazole was dissolved in 20 ml of THF. 0.9g of $NaBH_4$ were added under nitrogen and stirring. The suspension was cooled to 0°C and 0.86 ml of acetic acid dissolved in 5ml THF were slowly added, keeping the reaction temperature below 5°C. The reaction was stirred at 0°C for 30 minutes and for further 12 hours at room temperature. The reaction mixture was again cooled to 0°C and 50ml of sat. NH_4Cl solution were added carefully. The phases were separated and the aqueous layer extracted twice with EtOAc.

The combined organic layers were washed with brine, dried over MgSO4 and filtered. Removal of the solvent afforded 0.97g (of pure 2-(N-methylamino)-phenol.

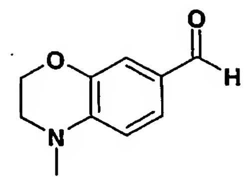
Step II: 4-Methyl-4H-benzo[1,4]oxazin-3-one

1g of 2-(N-methylamino)-phenol were dissolved in chloroform, followed by the addition of 10ml of sat. $NaHCO_3$ in water. To this suspension was added slowly under vigorous stirring a solution of 1g of 2-chloroacetylchloride in acetone. The reaction mixture was stirred for 2 hours at room temperature. The layers were separated. The organic layer was washed with water and dried over Na_2SO_4. After evaporating the solvent, the red oil was taken up in 30 ml DMF and 1g of K_2CO_3 were added and the slurry was heated at 70°C for additional 2 hours. The cyclization was followed by TLC. 200 ml of EtOAc were added and the organic layer was washed 3x with 0.1N HCl and 5x with brine. The remaining organic layer was dried over MgSO4 and filtrated. EtOAc was removed under reduced pressure affording 1.45g of pure 4-methyl-4H-benzo[1,4]oxazin-3-one.

Step III: 4-Methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-

1g of $AlCl_3$ were suspended in 10 ml DCM, 0.5 ml of nitromethane were added to dissolve $AlCl_3$, and the solution was cooled to 0°C. 4-Methyl-4H-benzo[1,4]oxazin-3-one (0.5g, 3.06 mmol) dissolved in DCM was added to the above solution and stirred for 15 minutes at 0°C. To this solution was further added 0.36ml of bis-chloromethyl-methylether in DCM. The reaction was stirred at 0°C for 15 minutes and at room temperature for 3h. The crude reaction mixture was then poured onto ice, the layers were separated and the organic phase was washed with $NaHCO_3$ and brine. After drying over $MgSO_4$ and filtration the solvent was evaporated, which afforded 0.43g of crude product. The dark oil was purified by flash chromatography using EtOAc and cyclohexane as eluents, affording 0.2g (37%) of 4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde as colourless solid. HPLC: 2.07 min. LC-MS: M/Z ESI: 1.31 min, 192.28 (M+1).

Intermediate 3: Preparation of 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde



Step I: 4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine

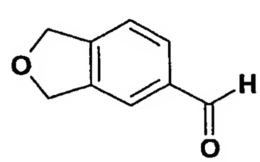
0.97g of 2-(N-methylamino)-phenol were dissolved in 50ml acetone, followed by the addition of 2g of K_2CO_3 dissolved in water. To this suspension was added slowly a solution of 2.66g of dibromoethane in acetone. The reaction mixture was stirred for 22 hours under reflux. Acetone was evaporated and 200ml of EtOAc were added and the organic layer was washed 3x with 0.1N HCl and 3x with brine. The remaining organic layer was dried over MgSO4 and filtrated. EtOAc was removed under reduced pressure affording 1g of pure 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine.

Step II: 4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde

4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine dissolved in 200ul DMF under Argon. $POCl_3$ was added under Argon. The reaction was heated and a closed vial at 90°C for 75min. 1ml of NaAc in water was added and stirred while a brown oil was formed. The oil was extracted with DCM. The organic layer was washed with brine, dried and evaporated to dryness, affording 0.18g (76%) of 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbaldehyde as colourless solid.

LC-MS: M/Z ESI: 1.37 min, 178.35 (M+1).

Intermediate 4: Preparation of 1,3-Dihydroisobenzofuran-5-carbaldehyde



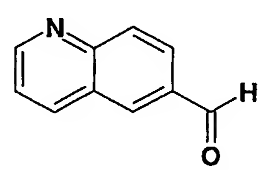
Step I (1,3-Dihydro-isobenzofuran-5-yl)-methanol

In a round bottom flask with reflux condenser were placed 1.0g of 3-Prop-2-ynyloxy-propyne and 2.08g of propargylic alcohol in 10ml ethanol, followed by the addition of 9.8mg of tris(triphenylphosphine)rhodium chloride (Wilkinson catalyst) at room temperature. The reaction was heated up to 70°C, while the reaction colour turned yellow rapidly. After 1 day stirring at r.t., TLC analysis showed complete conversion of the starting material. The solvent was evaporated, diluted with DCM and extracted with H_2O, dried over MgSO4. The brown mixture was purified by flash chromatography using 8/2 cyclohexane / AcOEt as mobile phase affording (1,3-Dihydro-isobenzofuran-5-yl)-methanol as a colourless pure solid (0.92g, 60%).

Step II: 1,3-Dihydroisobenzofuran-5-carbaldehyde

(1,3-Dihydro-isobenzofuran-5-yl)-methanol (440mg, 2.9mmol) was dissolved in 20 ml of DCM. 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin reagent) (1.3g, 3.2mmol) was added and the reaction was stirred at r.t. for 4h. The reaction mixture was diluted with ether and extracted 2x with NaOH 1N, 2x with H_2O and dried over $MgSO_4$. The crude product was sufficiently pure and used without any further purification. HPLC: 2.00 min. LC-MS: M/Z ESI: 1.50 min, 149.18 (M+1).

Intermediate 5: Preparation of Quinoline-6-carbaldehyde



Step I: Quinolin-6-yl-methanol

5g of methyl quinoline-6-carboxylate was dissolved in dry THF. Under Argon was added $LiAlH_4$ 1M in THF (2 eq.) at –20°C. The solution was stirred at that temperature for 1h.

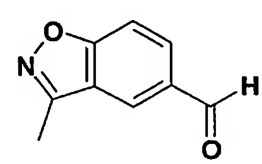
Isopropanol was slowly added and the crude filtered through celite and washed with DCM. Concentration gave 3.6 g (85%) of pure alcohol.
HPLC: 1.10 min. LC-MS: M/Z ESI: 0.91 min, 160.43 (M+1).

Step II: Quinoline-6-carbaldehyde

2g of quinolin-6-yl-methanol was dissolved in DCM.15g of MnO2 was added and the reaction mixture was stirred for 5h. The crude filtered through celite and washed extensively with DCM. Concentration gave 1.85g (93%) of pure aldehyde.
HPLC: 0.8 min. LC-MS: M/Z ESI: 1.07 min, 158.37 (M+1). ^{1}H NMR (DMSO-d6) δ 10.19 (s, 1H), 9.06 (t, J=3Hz, 1H), 8.6-8.66 (m, 2H), 8.15 (s, 2H), 7.68 (dd, J=3Hz, 9Hz, 1H).

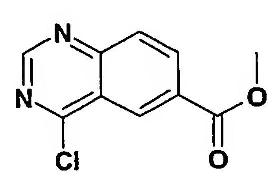
The following intermediate was synthesized accordingly using the suitable starting materials :

Intermediate 6: Preparation of 3-Methyl-benzo[d]isoxazole-5-carbaldehyde



HPLC: 2.06 min. LC-MS: M/Z ESI: 1.26 min, 162.31 (M+1). ^{1}H NMR (DMSO-d6) δ 10.10 (s, 1H), 8.52 (s, 1H), 8.16 (d, J=12Hz, 1H), 8.15 (s, 2H), 7.90 (d, J=9Hz, 1H), 2.63 (s, 3H).

Intermediate 7: Preparation of 4-Chloro-quinazoline-6-carboxylic acid methyl ester



Step I: 4-Nitro isophthalic acid

A mixture of 3-methyl-4-nitrobenzoic acid (150g, 0.825mol), pyridine (1.5L) and water (1.5L) was heated to reflux. To the hot reaction mixture was added $KMnO_4$ (10mol) portion wise and reflux for 72h. The hot reaction mixture was filtered through celite and washed with hot water. The filtrate was concentrated under vacuum, residue diluted with water (750mL) and acidified with con. HCl at 0°C. The solid obtained was filtered, washed with water and dried under vacuum to give 4-nitro isophthalic acid (98g, 56%).

TLC, Chloroform/Methanol, 7:3, R_f=0.2

Step II: 4-Amino isophthalic acid

To a solution of 4-nitro isophthalic acid (98g, 0.457mol) in methanol (5L) was added Pd/C (20%) and hydrogenated at RT for 4h. The reaction mixture was filtered through celite and filtrate concentrated under vacuum to give 4-amino isophthalic acid (72g, 87%) as a solid.

TLC, Chloroform/Methanol, 7:3, R_f=0.4

Step III: 4-Oxo-3,4-dihydroquinazoline-6-carboxylic acid

A mixture of 4-amino isophthalic acid (17g, 0.093mol) and formamide (85mL) was heated at 180°C for 5h. The reaction mixture was cooled to RT and added acetone. The solid precipitate thus obtained was stirred for 2h, filtered and dried to give 4-oxo-3,4-dihydroquinazoline-6-carboxylic acid (11g, 61%).

TLC, Chloroform/Methanol, 8:2, R_f=0.25

Step IV: 4-Oxo-3,4-dihydroquinazoline-6-methyl carboxylate

To a solution of 4-oxo-3,4-dihydroquinazoline-6-carboxylic acid (24g, 0.126mol) in dry methanol (800mL) was added thionylchloride (37g) at 5°C and then refluxed at 80°C for 5h. The reaction mixture was concentrated under vacuum and crude taken in ethylacetate (250mL). The organic layer was washed with 10% aqueous $NaHCO_3$, water, brine and dried. The solvent was removed under vacuum to give 4-oxo-3,4-dihydroquinazoline-6-methyl carboxylate (24g, 92%) as a solid.

TLC, Chloroform/Methanol, 8:2, R_f=0.6

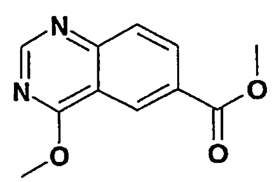
Step V: Methyl-4-chloroquinazoline-6-carboxylate

A mixture of 4-oxo-3,4-dihydroquinolin-6-methyl carboxylate (12g, 0.058mol) and phosphorylchloride (180mL) was heated to reflux for 7h. Excess phosphorylchloride was distilled off and crude taken in ethyla cetate (250mL). The organic layer was washed with 10% aqueous $NaHCO_3$ solution, water, brine and dried. The solvent was removed under vacuum and crude purified by column chromatography over silica gel (30% ethylacetate in pet. ether) to give methyl-4-chloroquinazoline-6-carboxylate (4.5g, 34%) as a solid.

TLC, pet. ether/EtOAc, 1:1, R_f=0.65

LC-MS: M/Z ESI: 1.50 min, 223.19 (M+1). ^{1}H NMR (DMSO-d6) δ 8.66 (d, J=1.9Hz, 1H), 8.39 (s, 1H), 8.30 (dd, J=0.6Hz, 8.5Hz, 1H), 7.79 (d, J=8.5Hz, 1H), 3.90 (s, 3H).

Intermediate 8: Preparation of 4-Methoxy-quinazoline-6-carboxylic acid methyl ester

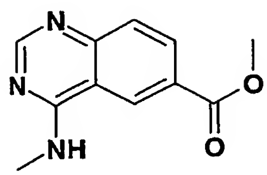


200 mg of methyl-4-chloroquinoline-6-carboxylate were strirred in 5 ml MeOH in the presence of 1eq. of DIEA at 60°C for 24h. MeOH was evaporated and the crude residue was taken up in EtOAc and washed with NH_4Cl affording a white solid sufficiently pure for the next step.

HPLC: 2.3 min. LC-MS: M/Z ESI: 1.19 min, 219.17 (M+1).

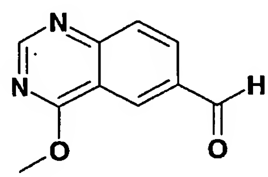
The following intermediate was synthesized according to the synthesis of intermediate 8:

Intermediate 9: Preparation of 4-Methylamino-quinazoline-6-carboxylic acid methyl ester



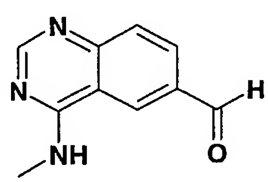
HPLC: 1.12 min. LC-MS: M/Z ESI: 1.06 min, 218.31 (M+1).

Intermediate 10: Preparation of 4-Methoxy-quinazoline-6-carbaldehyde



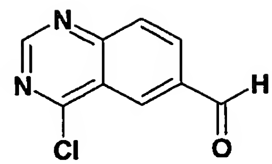
This intermediate was prepared according to the synthesis of intermediate 5 starting from 4-Methoxy-quinazoline-6-carboxylic acid methyl ester.
HPLC: 1.41 min. LC-MS: M/Z ESI: 1.24 min, 189.31 (M+1).

Intermediate 11: Preparation of 4-Methylamino-quinazoline-6-carbaldehyde



This intermediate was prepared according to the synthesis of intermediate 5 starting from 4-Methylamino-quinazoline-6-carboxylic acid methyl ester.
HPLC: 1.3 min. LC-MS: M/Z ESI: 0.90 min, 188.34 (M+1).

Intermediate 12: Preparation of 4-Chloro-quinazoline-6-carbaldehyde



Step I: 4-Chloroquinazoline-6-yl methanol

To a solution of methyl-4-chloroquinazoline-6-carboxylate (3.5g, 0.015mol) in dry THF (35mL) at –25°C was added DIBAL-H (4.4g, 0.031mol) and stirred at –25°C to RT for 2h. The reaction mixture was cooled to –10°C and quenched with 10% aqueous $NaHCO_3$ (9mL). The reaction mixture was extracted with ethylacetate (100mL), washed with water, brine and dried. The solvent was removed under vacuum to give 4-chloroquinoline-6-yl methanol (2g, 66%).

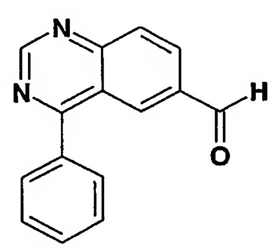
TLC, Chloroform/Methanol, 8:2, R_f=0.35

Step II : 4-Chloroquinazoline-6-carboxaldehyde

To a solution of 4-chloroquinazoline-6-yl-methanol (3.5g, 0.018mol) in dry CH_2Cl_2 (100mL) was added Dess-Martin periodinane (8.4g, 0.019mol) and stirred at RT for 30min. The reaction mixture was washed with 10% aqueous $NaHCO_3$ (75mL), water, brine and dried. The solvent was removed under vacuum to give 4-chloroquinazoline-6-carboxaldehyde (3g, 88%) as pale yellow solid.

TLC, Chloroform/Methanol, 9:1, R_f=0.6

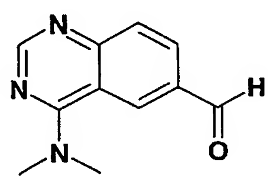
Intermediate 13: Preparation of 4-Phenyl-quinazoline-6-carbaldehyde



4-Chloro-quinazoline-6-carbaldehyde (50mg, 0.26mmol), $Pd(PPh_3)_4$ (13mg, 0.01mmol), phenylboronic acid (63mg, 0.52mmol) and sodium carbonate (sat. sol: 50ul) were heated up in toluene at 100°C for 12h. After evaporation of the solvents, the residue was taken up in ethyl acetate and washed with brine twice. Organic phases were then concentrated and raw materiel was purified on silica gel using DCM/EtOH 95:5 as eluents to give 50 mgs (82%) of the desired cpd with a 85% purity.

HPLC: 2.68 min. LC-MS: M/Z ESI: 1.25 min, 235.30 (M+1).

Intermediate 14: Preparation of 4-Dimethylamino-quinazoline-6-carbaldehyde



4-Chloro-quinazoline-6-carbaldehyde (200mg, 1mmol) was dissolved in 10ml dioxane. To this solution was added a solution of dimethylamine in water (5eq.). The mixture was stirred during 2h at r.t. Evaporation of the solvents and remaining amine under high vacuum afforded pure 4-Dimethylamino-quinazoline-6-carbaldehyde as a yellow solid, which was used for the next step without further purification (190mg = 91%).

HPLC: 0.91 min. LC-MS: M/Z ESI: 1.23 min, 202.33 (M+1). ^{1}H NMR (CDCl3) : δ 10.19 (s, 1H), 8.70 (s, 1H), 8.50 (d, J=3Hz, 1H), 8.15 (dd, J=3Hz, 9Hz, 1H), 7.88 (d, J= 9Hz, 1H).

The following intermediates were synthesized in a similar way using the suitable amines as nucleophiles.

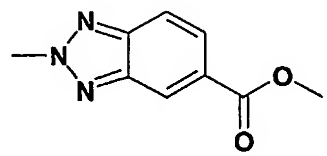
N°.	Intermediate	M/Z ESI:(M+1).
15	4-Piperidin-1-yl-quinazoline-6-carbaldehyde	242.27

16	4-Amino-quinazoline-6-carbaldehyde	174.18
17	4-Benzylamino-quinazoline-6-carbaldehyde	264.30
18	4-[(Pyridin-2-ylmethyl)-amino]-quinazoline-6-carbaldehyde	265.33
19	4-[(Pyridin-3-ylmethyl)-amino]-quinazoline-6-carbaldehyde	265.33
20	4-(4-Methyl-piperazin-1-yl)-quinazoline-6-carbaldehyde	257.31
21	4-Diethylamino-quinazoline-6-carbaldehyde	230.28
22	4-Morpholin-4-yl-quinazoline-6-carbaldehyde	244.26
23	1-(6-Formyl-quinazolin-4-yl)-piperidine-3-carboxylic acid ethyl ester	314.36
24	1-(6-Formyl-quinazolin-4-yl)-pyrrolidine-2-carboxylic acid tert-butylester	328.39
25	1-(6-Formyl-quinazolin-4-yl)-piperidine-4-carboxylic acid ethyl ester	314.36
26	4-(4-Hydroxy-piperidin-1-yl)-quinazoline-6-carbaldehyde	258.30
27	4-(4-Methyl-piperidin-1-yl)-quinazoline-6-carbaldehyde	256.32
28	4-(4-Phenethyl-piperidin-1-yl)-quinazoline-6-carbaldehyde	346.42
29	4-(4-Benzyl-piperidin-1-yl)-quinazoline-6-carbaldehyde	332.40
30	4-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-quinazoline-6-carbaldehyde	336.38
31	4-(4-Pyrimidin-2-yl-piperazin-1-yl)-quinazoline-6-carbaldehyde	321.36

Intermediates 32: Preparation of Methyl-benzotriazole-5-carboxylic acid methyl ester

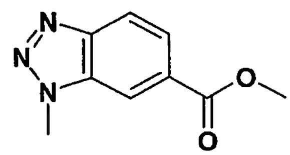
1 g of Benzotriazole-5-carboxylic acid methyl ester (5.64mmol) was dissolved in 20ml DMF at 0°C. To this solution was added 1eq. of NaH (60%) at 0°C. The mixture was stirred for 30min at 0°C, 801 mg (1eq.) of Methyliodide were slowly added, and the resulting reaction mixture was stirred for 2h at rt. EtOAc was added and the organic layer was washed extensively with brine and water, dried over MgSO4 and filtered to afford 1g of crude Methyl-benzotriazole-5-carboxylic acid methyl ester as three different regio-isomers. The separation was performed on silica gel using EtOAc/CH 3:7 as eluents.

Intermediate 32a: 2-Methyl-2H-benzotriazole-5-carboxylic acid methyl ester



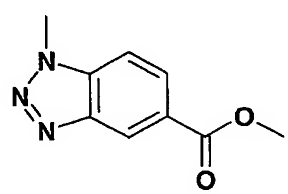
2-Methyl-2H-benzotriazole-5-carboxylic acid methyl ester eluted as first fraction (250mg, 22%). HPLC: 2.32 min. ^{1}H NMR (DMSO-d6) δ 8.56 (s, 1H), 8.02 (d, J=9Hz, 1H), 7.93 (d, J=9Hz, 1H), 4.55 (s, 3H), 3.90 (s, 1H).

Intermediate 32b: 3-Methyl-3H-benzotriazole-5-carboxylic acid methyl ester



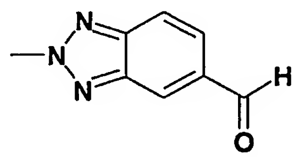
3-Methyl-3H-benzotriazole-5-carboxylic acid methyl ester eluted as 2nd fraction (130mg , 12%). HPLC: 2.03 min. ^{1}H NMR (DMSO-d6) δ 8.56 (s, 1H), 8.13 (d, J=6Hz, 1H), 7.93 (d, J= 9Hz, 1H), 4.39 (s, 3H), 3.92 (s, 3H).

Intermediate 32c: 1-Methyl-1H-benzotriazole-5-carboxylic acid methyl ester



1-Methyl-1H-benzotriazole-5-carboxylic acid methyl ester eluted as 3rd fraction (135mg , 12%). HPLC: 2.03 min. ^{1}H NMR (DMSO-d6) δ 8.62 (s, 1H), 8.11 (d, J=9Hz, 1H), 7.97(d, 9Hz, 1H), 4.35 (s, 3H), 3.90 (s, 3H).

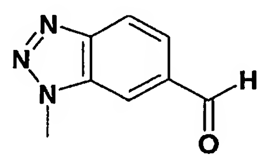
Intermediate 33: 2-Methyl-2H-benzotriazole-5-carbaldehyde



This intermediate has been synthesized according to the synthesis of intermediate 5 using 2-Methyl-2H-benzotriazole-5-carboxylic acid methyl (intermediate 32a) ester as starting point.

HPLC: 1.88 min. ^{1}H NMR (DMSO-d6) δ 10.12 (s, 1H), 8.65 (s, 1H), 8.06 (d, *J*=9Hz, 1H), 7.85 (d, *J*=9Hz, 1H), 4.57 (s, 3H).

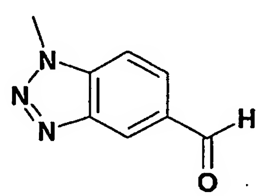
Intermediate 34: 3-Methyl-3H-benzotriazole-5-carbaldehyde



This intermediate has been synthesized according to the synthesis of intermediate 5 using 3-Methyl-3H-benzotriazole-5-carboxylic acid methyl ester (intermediate 32b) as starting point.

HPLC: 1.49 min. ^{1}H NMR (DMSO-d6) δ 10.18 (s, 1H), 8.54 (s, 1H), 8.20 (d, *J*=9Hz, 1H), 7.88(d, *J*=9Hz, 1H), 4.41 (s, 3H).

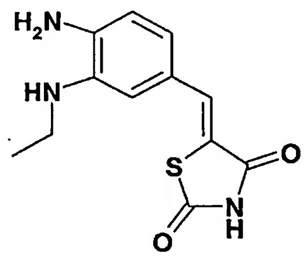
Intermediate 35: 1-Methyl-1H-benzotriazole-5-carbaldehyde



This intermediate has been synthesized according to the synthesis of intermediate 5 using 1-Methyl-1H-benzotriazole-5-carboxylic acid methyl ester as starting point (intermediate 32c).

HPLC: 1.49 min. LC-MS: M/Z ESI: 1.07 min, 162.32 (M+1). . ^{1}H NMR (DMSO-d6) δ 10.13 (s, 1H), 8.70 (s, 1H), 8.05 (s, 2H), 4.36 (s, 3H).

Intermediate 36: 5-(4-Amino-3-ethylamino-benzylidene)-thiazolidine-2,4-dione



Step I : 3-Fluoro 4-nitro benzyl alcohol (*Bioorg. Med. Chem. 7*, 1999, 2647)

To an ice-cooled suspension of $NaBH_4$ (204mg, 5.4mmol, 2eq.) in THF (10mL) was added dropwise 3-fluoro 4-nitro benzoic acid (500mg, 2.7mmol, 1eq.) in THF (10mL) over 30 minutes. BF_3-Et_2O (7.3mmol, 2.7eq.) was then added dropwise over 30 minutes. The solution was stirred at room temperature over night. 1N HCl was added dropwise to quench $NaBH_4$ excess. The solvent was removed *in vacuo*, the residue dissolved in DCM, washed with water, brine. The organic layer was then dried over $MgSO_4$ and the solvent removed *in vacuo* to give 425 mg of 3-fluoro 4-nitro benzyl alcohol (92% yield). The compound was used in the following step with no further purification.

^{1}H NMR: δ=(400 MHz, $CDCl_3$): 7.97 (m, 1H), 7.28 (m, 1H), 7.18 (m, 1H), 4.75 (m, 2H).

Step II: 3-Fluoro 4-nitro benzyl aldehyde

3-fluoro 4-nitro benzyl alcohol (116mg, 0.68mmol, 1eq.) was dissolved in DCM (10ml) and treated with MnO_2 (580mg, 6.73mmol, 10eq.) and the suspension stirred at room

temperature over night. MnO_2 was filtered off the suspension using celite and the solvent evaporated to give the corresponding aldehyde as a white solid (66% yield).

^{1}H NMR: δ=(400 MHz, $CDCl_3$): 9.98 (s, 1H, C*HO*), 8.08 (m, 1H, ArH), 7.78 (m, 2H, ArH).

Step III: 5-(3-Fluoro-4-nitro-benzylidene)-thiazolidine-2,4-dione (*J. Med. Chem.* 37, 2, 1994, 322)

A mixture of 3-fluoro 4-nitro benzyl aldehyde (280mg, 1.65mmol, 1eq.), thiazolidine-dione (193mg, 1.65mmol, 1eq.) and β-alanine (95mg, 1.1mmol, 0.65eq.) in acetic acid (5mL) was stirred over night at 100°C. The cooled reaction mixture was added to water and stirred for 1 hour. The precipitated product was filtered and washed with water and dried to yield the final product as a yellow/orange solid (77% yield).

^{1}H NMR: δ=(400 MHz, $(CD_3)_2CO$): 8.0 (m, 1H, ArH), 7.68 (m, 2H, ArH), 7.53 (s, 1H, C*H*=C).

Step IV: 5-(3-Ethylamino-4-nitro-benzylidene)-thiazolidine-2,4-dione

5-(3-Fluoro-4-nitro-benzylidene)-thiazolidine-2,4-dione (200mg, 0.75mmol, 1eq.), was dissolved in DME (6mL) and TEA (208μL, 1.5mmol, 2eq.) and a solution of ethylamine (2eq.) was added. The reaction mixture was shaken at 60°C over night. The solvent was removed *in vacuo* and residue dissolved in ethyl acetate and washed with 10% ammonium chloride aqueous solution. The organic layer was dried on Na_2SO_4 and the solvent evaporated to give the corresponding aniline derivative as either red oil, which was used for the next step without further purification.

Step V: 5-(3-Ethylamino-4-amino-benzylidene)-thiazolidine-2,4-dione

To a stirred solution of 5-(3-Ethylamino-4-nitro-benzylidene)-thiazolidine-2,4-dione in THF, a solution of sodium hydrosulfite (3 eq.) in water was slowly added followed by an aqueous solution of K_2CO_3. The reaction mixture was refluxed over night. THF was removed *in vacuo* and residue extracted with ethyl acetate The organic layer was dried on

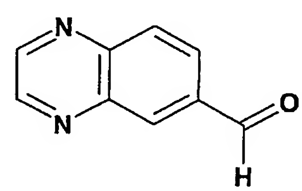
Na_2SO_4 and the solvent evaporated to give the corresponding aniline derivative, which was used without any further purification.

The following intermediates were synthesized in a similar way using the suitable amines as nucleophiles as described in step IV of intermediate 36. The so-obtained 3-alkylamino-4-nitro-benzylidene)-thiazolidine-2,4-diones were reduced as described in step V of intermediate 36 affording 3-alkylamino-4-amino-benzylidene)-thiazolidine-2,4-diones.

N°.	Intermediate	M/Z ESI:(M+1)
37	5-[4-Amino-3-(4-phenyl-butylamino)-benzylidene]-thiazolidine-2,4-dione	368.2
38	5-{4-Amino-3-[2-(4-trifluoromethyl-phenyl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	408.12
39	5-{4-Amino-3-[2-(4-hydroxy-phenyl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	356.13
40	4-[2-Amino-5-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenylamino]-cyclohexanecarboxylic acid methyl ester	376.35
41	5-{4-Amino-3-[2-(1H-indol-3-yl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	409.21
42	5-{4-Amino-3-[(1-methyl-1H-pyrazol-4-ylmethyl)-amino]-benzylidene}-thiazolidine-2,4-dione	331.1
43	5-{4-Amino-3-[2-(3,4-dimethoxy-phenyl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	400.21
44	5-[4-Amino-3-(4-trifluoromethyl-benzylamino)-benzylidene]-thiazolidine-2,4-dione	394.15
45	4-[2-Amino-5-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenylamino]-cyclohexanecarboxylic acid	362.17
46	5-(4-Amino-3-isobutylamino-benzylidene)-thiazolidine-2,4-dione	292.22

47	5-[4-Amino-3-(2-benzo[1,3]dioxol-4-yl-ethylamino)-benzylidene]-thiazolidine-2,4-dione	384.26
48	5-{4-Amino-3-[2-(2-phenoxy-phenyl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	432.28
49	5-[4-Amino-3-(3,3-diphenyl-propylamino)-benzylidene]-thiazolidine-2,4-dione	430.27
50	5-(4-Amino-3-prop-2-ynylamino-benzylidene)-thiazolidine-2,4-dione	274.21
51	5-[4-Amino-3-(2-methoxy-benzylamino)-benzylidene]-thiazolidine-2,4-dione	356.23
52	5-{4-Amino-3-[(furan-3-ylmethyl)-amino]-benzylidene}-thiazolidine-2,4-dione	316.21
53	5-(4-Amino-3-propylamino-benzylidene)-thiazolidine-2,4-dione	278.16
54	5-{4-Amino-3-[2-(4-phenoxy-phenyl)-ethylamino]-benzylidene}-thiazolidine-2,4-dione	432.23

Intermediate 55: Quinoxaline-6-carbaldehyde



Step I: Quinoxaline-6-carbonyl chloride

In a 1l 3 neck flask was placed Quinoxaline-6-carboxylic acid (20.2 g) in 500 ml of THF. To this solution was slowly added thionylchloride (42ml, 5eq.). The reaction mechanically stirred was warmed up to reflux and followed by HPLC quenching the sample with NH_4OH. After 3h at reflux no more starting material was present, the solvent was removed under reduced pressure and $SOCl_2$ was chased with toluene 3 times. The solid was suspended in 100 ml EtOAc and filtered to obtain 23.47g of a beige solid.

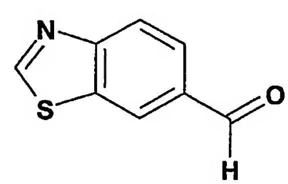
HPLC: 1.114 min. ^{1}H NMR (DMSO-d6) δ 9.01-7.40 (m, 5H).

Step I: Quinoxaline-6-carbaldehyde

In a 1l 3-neck flask under argon was placed Quinoxaline-6-carbonyl chloride in 600ml of DME. To this solution was added lithium tri-tert-butoxyaluminohydride (1 eq.) at –78°C over 1.5 h. The reaction was kept at that temperature for 5h. Then ice was added, and the reaction was diluted with AcOEt and filtrated over celite. The two layers were separated and the organic phase was washed with $NaHCO_3$ sat. Quinoxaline-6-carbaldehyde was obtained upon evaporating the solvent in 73% yield as yellowish solid.

HPLC: 1.49 min. LC-MS: M/Z ESI: 0.81 min, 159.37(M+1). ^{1}H NMR (CDCl3) δ 10.28 (s, 1H), 8.97 (s, 2H), 8.61 (s, 1H), 8.27 (q, 6Hz, 9Hz, 2H).

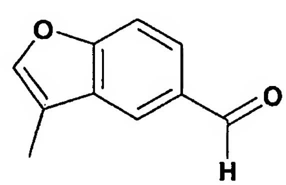
Intermediate 56: Benzothiazole-6-carbaldehyde



This intermediate was synthesized as seen in the synthesis of intermediate 55 starting from Benzothiazole-6-carboxylic acid. The overall yield was 38%.

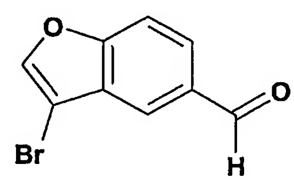
HPLC: 1.92 min. LC-MS: M/Z ESI: 0.97 min, 164.27 (M+1). ^{1}H NMR (DMSO-d6) δ 10.1 (s, 1H), 9.60 (s, 1H), 8.60 (s, 1H), 8.20 (m, 1H), 8.10 (d, 1H).

Intermediate 57: 3-Methyl-benzofuran-5-carbaldehyde



This intermediate was accessed through the same route as intermediate 1 using Ethyl-2-acetyl-4-bromophenoxy acetate as starting material. Overall yield 50%.
LC-MS: M/Z ESI: 1.55 min, 161.34 (M+1). ^{1}H NMR (DMSO-d6) δ 10.1 (s, 1H), 8.21 (d, *J*=1.5Hz 1H), 7.92 (d, *J*=1.3Hz, 1H), 7.88-7.84(dd, *J*=1.6Hz, 1H), 7.73-7.71 (d, *J*=8.5Hz, 1H), 2.25 (s, 3H).

Intermediate 58: 3-Bromo-benzofuran-5-carbaldehyde



Step I: 2,3-Dibromo-2,3-dihydro-benzofuran-5-carbaldehyde

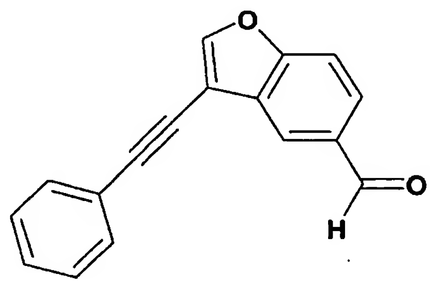
Intermediate 1 (2g, 13.7mmol) was dissolved in 10ml CHCl3 and cooled to –10°C. To this was added a solution of Br_2 in $CHCl_3$ (1.55 eq., c=4.162mol/l). The reaction mixture turned dark and was allowed to reach r.t. during 1h. HPLC indicated complete addition of bromine. The solvent and remaining bromine were evaporated under reduced pressure affording a reddish oil (4.1g = 90%), which was used for the next step without further purification.
HPLC: 3.43 min

Step II: 3-Bromo-1-benzofuran-5-carbaldehyde

To a solution of 2,3-dibromo-2,3-dihydro-1-benzofuran-5-carbaldehyde (4.1g) in dry ethanol (15mL) was added a solution of KOH (2.2 eq.) in dry ethanol (14mL) and refluxed at 70°C for 1h. The reaction mixture was cooled, diluted with water and extracted with EtOAc (3x50mL). The organic layer was washed with water, brine and dried. The solvent was removed under vacuum and the residue was purified by flash chromatography (pet. ether/EtOAc 99.5:0.5) to give the title compound as a pale yellow solid (2.91g (80%pure), yield=78%).

HPLC: 3.35 min. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.12 (s, 1H), 8.47 (s, 1H), 8.14 (d, *J*=1.5 Hz, 1H), 7.97 (dd, *J*=8.6, 1.5 Hz, 1H), 7.87 (d, J=8.6 Hz, 1H).

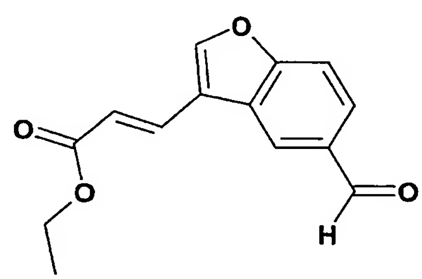
Intermediate 59: 3-Phenylethynyl-benzofuran-5-carbaldehyde



In a dry flask 3-Bromo-1-benzofuran-5-carbaldehyde (1g, 4.4mmol) were dissolved in anhydrous THF (50 ml). To this was added under Argon Bis (triphenylphosphine) palladium(II) chloride (160mg, 0.2mmol), TEA (2.81mL, 5eq.), CuI (40mg, 0.2mmol) and Phenylacetylene (897mg, 8.8mmol). The reaction was heated at 55°C for 2 days. The crude was filtered through celite and purified on silicagel using as eluent cyclohexan-ethyl acetate (7-3) affording 680mg (yield: 56%)

HPLC: 4.71 min. ^{1}H NMR (DMSO-d6) δ 10.14 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 7.97 (dd, *J*=1.5Hz, 8.3Hz, 1H), 7.90 (d, *J*=8.6Hz, 1H), 7.65 (m, 2H), 7.46 (m, 3H).

Intermediate 60: 3-(5-Formyl-benzofuran-3-yl)-acrylic acid ethyl ester

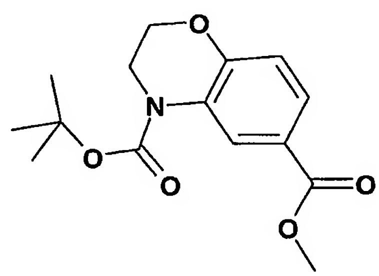


In a sealed tube 3-Bromo-1-benzofuran-5-carbaldehyde (500mg, 2.22mmol) was dissolved in 7 ml of ACN. To this solution was added PPh_3 (1.16g, 4.44mmol), Pd(II)acetate (500mg,

2.2mmol), Et3N (073mL, 5.55mmol) and finally acrylic acid ethyl ester (2.41ml, 22mmol). The tube was sealed and the reaction was heated at 120°C for one hour. The crude was filtered on celite to eliminate inorganic contaminations. The solvents were evaporated and the crude was purified by silicagel chromatography using cyclohexane-AcOEt 95-5 to 50-50. A pale yellow solid was obtained (400mg, yield:42%).

HPLC: 3.69 min. ^{1}H NMR (DMSO-d6) δ 10.15 (s, 1H), 8.70 (s, 2H), 7.97 (d, *J*=9Hz 1H), 7.88 (s, 1H), 7.82 (s, 1H), 6.76 (d, *J*=15Hz, 1H), 4.23 (q, *J*=6Hz, 12Hz, 2H), 1.28 (t, *J*=9Hz, 3H).

Intermediate 61: 2,3-Dihydro-benzo[1,4]oxazine-4,6-dicarboxylic acid 4-tert-butyl ester 6-methyl ester



Step I: 3-Amino-4-hydroxy-benzoic acid methyl ester

To a 2000ml three-necked flask containing 3-Nitro-4-hydroxy-benzoic acid methyl ester (43g, 218mmol) in MeOH (860ml; 20vols) was added palladium on carbon in water (2g in 10ml of water). Ammonium formiate (68.76g, 5eq.) was added in a single portion under stirring. After 2 to 3 minutes a suspension was observed, and temperature rised from 20°C to 30°C. Ice bath was used to cool reaction mixture to 20°C and the reaction was stirred at 20°C for 40minutes until completion (no more yellow color). Reaction mixture was filtered on silica plug, rinsed with MeOH, and the filtrate was concentrated under vacuum to give a green oil which was taken up in ethyl acetate (400ml). The organic phase was washed twice with water, dried over $MgSO_4$, filtered and concentrated to give a cream solid m=31.35g (86%).

LC-MS: M/Z ESI: 0.81 min, 168.37 (M+1)

Step II: 3,4-Dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid methyl ester*hydrochloride

To a 2000ml three-necked flask under N_2 containing 3-Amino-4-hydroxy-benzoic acid methyl ester (31.35g, 187mmol) in anhydrous DMF (630ml; 20vols) at RT, was added K_2CO_3 (103g, 4eq.) in one portion followed by 1,2dibromoethane (65ml, 4eq.) in one portion. The reaction mixture was stirred at 70°C for 12h. Temperature was allowed to cool down to RT, and HCl1N was added until pH=8, and extraction was performed using diethyl ether (3*200ml). The organic phase was washed with water (2*200ml) and dried over $MgSO_4$ and concentrated to afford a brown red oil with solid, which was taken up again in diethyl ether (450ml) and THF (50ml) and filtered to remove a white solid. To the filtrate was added HCl1N, and diethyl ether (130ml) was added, suspension was stirred at RT for 5 minutes and filtered to give 27.6g of crude product. The aqueous phases were again extracted with ethyl acetate to afford additional 6.23g of product. The combined fractions (32g) were recrystallised from EtOH (420ml; 13vols) to give after filtration and drying a white powder (19.47g (16.37g free base)), yield = 40%.

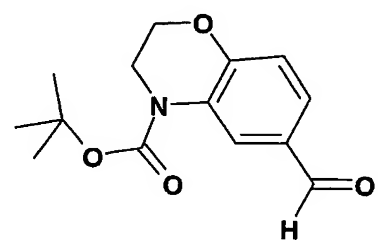
HPLC: 1.954 min. LC-MS: M/Z ESI: 1.27 min, 194.45 (M+1).

Step III: 2,3-Dihydro-benzo[1,4]oxazine-4,6-dicarboxylic acid 4-tert-butyl ester 6-methyl ester

To a 500ml three-necked flask containing 3,4-Dihydro-2H-benzo[1,4]oxazine-6-carboxylic acid methyl ester*hydrochloride in suspension in THF (145ml; 10 vols) under N_2, DIEA (27ml, 2.5eq.) was added in one portion at RT and partial solubilisation was observed. Boc andydride /(16.4g, 1.2 eq.) was added in one portion and the reaction was stirred at 65°C for 5 days. During that time several small portions of 0.2 eq. of Boc_2O and DIEA were added. THF was removed under vacuum and the residue was taken up in DCM 150ml The organic phase was washed with a saturated solution of $NaHCO_3$ and then with brine. After drying over $MgSO_4$ and filtration, volatiles were removed under vacuum and the residue was recristallised from EtOH (80ml) to give cream crystals (14.8g, 76%).

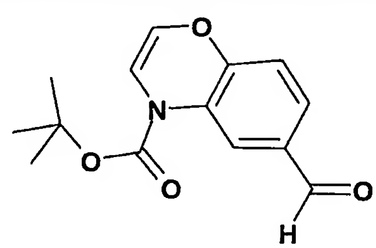
HPLC: 4.038 min. ^{1}H NMR (CDCl3) δ 8.49 (s, 1H), 7.68 (dd, *J*=3Hz, 9Hz, 1H), 6.89 (d, *J*=9Hz, 1H), 4.30 (q, *J*=3Hz, 9Hz, 2H), 3.89 (m, 5H), 1.62 (s, 9H).

<u>Intermediate 62: 6-Formyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester</u>



This intermediate was accessed through oxido-reduction as described for intermediate 5. HPLC: 3.727 min. LC-MS: M/Z ESI: 1.81 min, 264.34 (M+1). ^{1}H NMR (DMSO-d6) δ 9.83 (s, 1H), 8.35 (s, 1H), 7.53 (d, *J*=6Hz, 1H), 7.05 (d, *J*=9Hz, 1H), 4.31 (t, *J*=3Hz, 2H), 3.83 (t, *J*=6Hz, 2H), 1.50 (s, 9H).

<u>Intermediate 63: 6-Formyl-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester</u>



<u>Step I: 2,3-Dibromo-2,3-dihydro-benzo[1,4]oxazine-4,6-dicarboxylic acid 4-tert-butyl ester 6-methyl ester</u>

To a solution of 2,3-Dihydro-benzo[1,4]oxazine-4,6-dicarboxylic acid 4-tert-butyl ester 6-methyl ester (500mg, 1.7mmol) in dry carbon tetrachloride (20ml) was added N-Bromosuccinimide (667mg, 3.75mmol) and a catalytic amount of benzoylperoxide. The resulting mixture was stirred and heated with a bulp lamp (100W) at reflux for 45min. The mixture was allowed to cool and the succinimide was filtered off. The filtrate was evaporated to yield an oil (767mg, 99%) sufficiently pure to be used for the next step.

HPLC: 3.978 min

Step II: Benzo[1,4]oxazine-4,6-dicarboxylicacid 4-tert-butyl ester 6-methyl ester

2,3-Dibromo-2,3-dihydro-benzo[1,4]oxazine-4,6-dicarboxylic acid 4-tert-butyl ester 6-methyl ester (767mg, 1.7mmol) from proceeding step was stirred in acetone (14ml) at RT for 2h with NaI (1.27g, 8.5mmol). The solvent was removed, EtOAc, water and 1 M sodium thiosulfate were added. After separating phases the organic layer was washed with brine. The solvent was concentrated and the crude was purified on silica gel using CH/EtOAc 7:3 to obtain a colorless oil (456mg, 92%).

HPLC: 4.386 min.

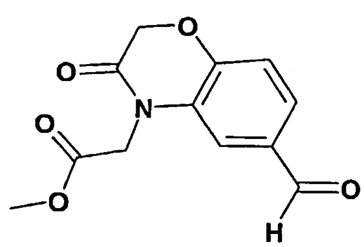
Step III: 6-Hydroxymethyl-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

Step IV: 6-Formyl-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester

Step III and IV were carried out according to the synthesis of intermediate 5.

HPLC: 3.388 min.

Intermediate 64: (6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-acetic acid methyl ester



Step I: Methyl-3-amino-4-hydroxybenzoate

To a solution of 3-amino-4-hydroxybenzoic acid (100g, 0.65mol) in methanol (1.5L) was added thionylchloride (233g, 1.96mol) drop-wise at 5-10°C with stirring and allowed to reflux at 65°C for 16h. Excess methanol and thionylchloride was distilled off and crude dissolved in ethylacetate (500mL). The organic layer was washed with 5% aqueous

$NaHCO_3$ solution, water, brine and dried. The solvent was removed under vacuum to give methyl-3-amino-4-hydroxybenzoate (105g, 95%).

Step II: Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carboxylate

To a mixture of methyl-3-amino-4-hydroxybenzoate (105g, 0.62mol) and benzyltriethylammonium chloride (142g, 0.62mol) in dry $CHCl_3$ (1.5L) was added $NaHCO_3$ (211g, 2.5mol) with stirring. The reaction mixture was cooled to –5°C, added chloroacetylchloride (85g, 0.75mol) in dry $CHCl_3$ (350mL) over a period of 1.5h at the same temperature. The reaction mixture was then heated to 55°C for 16h. The solvent was removed under vacuum, added water (3L) and filtered off the solid. The solid product was dried and recrystallised from ethanol to give methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carboxylate (108g, 83%).

Step III: 6-(Hydroxymethyl)-2H-1,4-benzoxazin-3(4H)-one

A solution of methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carboxylate (30g, 0.145mol) in dry CH_2Cl_2 (500mL) was cooled to –78°C and added DIBAL-H (51g, 0.36mol) over a period of 45min and then stirred at the same temperature for 14h. The reaction mixture was quenched with 1.5N HCl and filtered off the solid product. The solid compound was dried under vacuum to give 6-(hydroxymethyl)-2H-1,4-benzoxazin-3(4H)-one (18g, 69%).

Step IV: TBDMS-6-(hydroxymethyl)-2H-1,4-benzoxazin-3(4H)-one

To a solution of 6-(hydroxymethyl)-2H-1,4-benzoxazin-3(4H)-one (18g, 0.1omol) in dry DMF (250mL) was added imidazole (13.7g, 0.2mol) and stirred at 0°C for 30min. To the above reaction mixture was added TBDMSiCl (23g, 0.15mol) in portions and stirred at RT for 4h. The reaction mixture was diluted with water and filtered off the solid obtained. The solid was dried under vacuum to give TBDMS-6-(hydroxymethyl)2H-1,4-benzoxazin-3(4H)-one (24.5g, 83%).

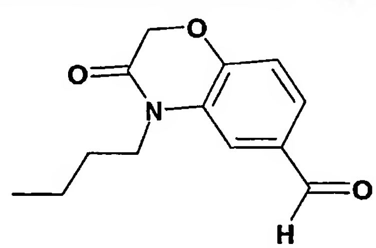
Step V: Methyl-[6-(hydroxymethyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate

To a suspension of NaH (0.3g, 0.01mol) in dry DMF (15mL) was added TBDMS-6-(hydroxymethyl)2H-1,4-benzoxazin-3(4H)-one (2g, 0.0068mol) at 0°C with stirring and allowed to stir at RT for 2h. The reaction mixture was cooled to 0°C, added methylchloroacetate (1g, 0.0088mol) and stirred at RT for 12h. The reaction mixture was further cooled to 0°C, added 50mL of 1.5N HCl solution and stirred at RT for 12h. The reaction mixture was diluted with water (200mL), extracted with ethylacetate (3x150mL). The combined organic layer was washed with 10% aqueous $NaHCO_3$ solution, brine and dried. The solvent was removed under vacuum and crude purified by column chromatography over silica gel ($CHCl_3$/Methanol, 99.5:0.5) to give methyl-[6-(hydroxymethyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate (1.2g, 70%).

Step VI: Methyl-[6-(Formyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate

A mixture of PCC (4.2g, 0.019mol) and celite (4g) in dry CH_2Cl_2 (100mL) was cooled to 0°C and slowly added a solution of methyl-[6-(hydroxymethyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]acetate (1.2g, 0.0048mol) in CH_2Cl_2 (30mL) under N_2. The reaction mixture was stirred at RT for 2h, passed through celite, washed with CH_2Cl_2 (50mL) and concentrated to give crude product, which was purified on silica gel affording 1.05g (87%). LC-MS: M/Z ESI: 1.15 min, 250.41 (M+1). ^1H NMR (DMSO-d6) δ 9.88 (s, 1H), 7.65-7.60 (m, 2H), 7.24 (d, J=8.1Hz, 1H), 4.85 (d, J=9.9Hz, 4H), 3.71 (s, 3H).

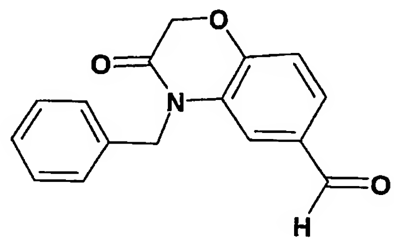
Intermediate 65: 4-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde



This intermediate was synthesized according to the synthesis of intermediate 2. Overall yield 33%.

LC-MS: M/Z ESI: 1.60 min, 234.35 (M+1). ^{1}H NMR (DMSO-d6) δ 7.66 (d, *J*=0.7Hz, 1H), 7.58 (dd, *J*=1.7Hz, 8.1Hz, 1H), 7.18 (d, *J*=8.2Hz, 1H), 4.77 (s, 2H), 3.96 (t, *J*=7.3Hz, 1H), 1.61-1.51 (m, 3H), 1.97-1.27 (m, 3H), 0.91 (t, *J*=7.3Hz, 3H).

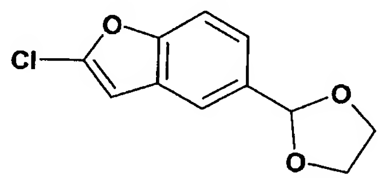
Intermediate 66: 4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde



This intermediate was synthesized according to the synthesis of intermediate 2. Overall yield 29%.

^{1}H NMR (DMSO-d6) δ 9.78 (s, 1H), 7.58 (dd, *J*=1.5Hz, 7.9Hz, 1H), 7.47 (d, *J*=1.9Hz, 7.40-7.18 (m, 6H), 5.22 (s, 2H), 4.95 (s, 2H), 3.3 (d, *J*=7.2Hz, 1H).

Intermediate 67: 2-Chloro-5-[1,3]dioxolan-2-yl-benzofuran



Step I: 5-[1,3]Dioxolan-2-yl-benzofuran

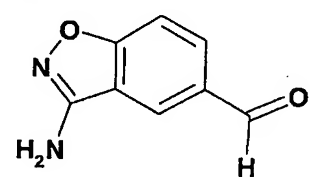
A mixture of benzofuran-5-carbaldehyde (150mg, 1.03mmol), ethylene glycol (230ul, 4eq), trimethyl orthoformate (123ul, 1.1eq) and tetrabutylammonium tribromide (49mg, 0.1 eq) was stirred at room temperature for one night. Some starting material could be detected by TLC. However, the reaction mixture was poured into saturated $NaHCO_3$ solution and the product was extracted with ethyl acetate. Combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated to give a crude product, which was purified by flash chromatography using cyclohexane/ethyl acetate 20:0.75 as solvents. The title compounds was obtained in 36% yield (70 mg).

LC-MS: M/Z ESI: 1.51 min, 191.30 (M+1).

Step II: 2-Chloro-5-[1,3]dioxolan-2-yl-benzofuran

5-[1,3]Dioxolan-2-yl-benzofuran (50mg, 0.26mmol) was dissolved in THF (2 mL) and the solution was cooled down to –78°C. Butyl lithium (180uL, 1.1eq.) was added dropwise. This mixture was stirred 30 min at 25°C. Then the reaction mixture was cooled down to –78°C and NCS (39mg, 1.1eq.) dissolved in 1 mL THF was added dropwise to the reaction mixture. After 1h30 at –78° C only small amount of starting material could be detected. The temperature was increased slowly to room temperature overnight. Water and ethyl acetate were added to the mixture and the aqueous layer was extracted 3 times. Combined organic phases was dried over $MgSO_4$, filtrated and evaporated to give 2-Chloro-5-[1,3]dioxolan-2-yl-benzofuran (48.1 mg, 81%) sufficiently pure to be used in the next step.
LC-MS: M/Z ESI: 1.77 min, 225.23 (M+1).

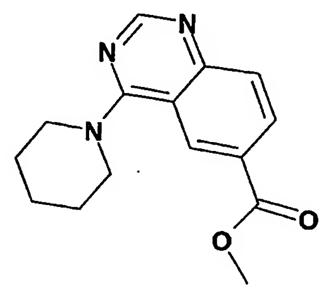
Intermediate 68: 3-Amino-benzo[d]isoxazole-5-carbaldehyde



Kaiser oxime resin (Novabiochem 01-64-0188) (250mg) was washed with DCM and THF (3 times 5min), 2ml of THF was added followed by the addition of 300ul of potassium-tert.butoxide (1M in THF, 1.2eq.) at r.t.. The resin turned orange and was shaken in the Quest210™ for 15'. 2-Fluoro-5-formyl-benzonitrile (75mg, 2eq.) in 1ml THF was added and the reaction was heated at 55°C for 12h. The resin was washed with DCM, MeOH, water (each 2 x 5minutes) and MeOH (4 x 5min). The resin was dried at 40°C with a flow of Argon for 30' before cleaving.

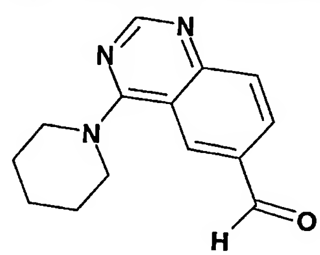
The so dried resin was treated with TFA/5N HCl 4:1 (2.5 ml) for 2h at 55°C. The solution was collected in 20ml vials and the resin was washed twice with 4ml of DCM. The collected fractions were evaporated with the Genevac HT4 to dryness affording: 37 mg (92%) of pure 3-Amino-benzo[d]isoxazole-5-carbaldehyde.
HPLC: 1.47 min. LC-MS: M/Z ESI: 0.82 min, 163.26 (M+1).

Intermediate 69: 4-Piperidin-1-yl-quinazoline-6-carboxylic acid methyl ester



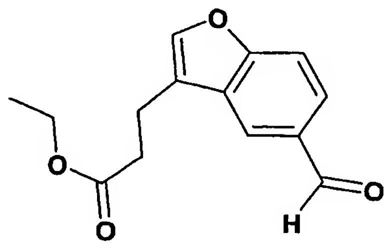
This intermediate was prepared according to the synthesis of intermediate 8 starting from 4-Chloro-quinazoline-6-carboxylic acid methyl ester (intermediate 7).
HPLC: 1.81 min. LC-MS: M/Z ESI: 1.78 min, 272.32(M+1).

Intermediate 70: 4-Piperidin-1-yl-quinazoline-6-carbaldehyde



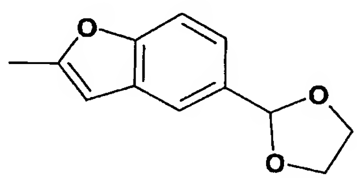
This intermediate was prepared according to the synthesis of intermediate 5 starting from 4-Piperidine-quinazoline-6-carboxylic acid methyl ester (intermediate 71).
HPLC: 1.36 min. LC-MS: M/Z ESI: 1.40 min, 242.32(M+1).

Intermediate 71: 3-(5-Formyl-benzofuran-3-yl)-propionic acid ethyl ester



100mg of 3-(5-Formyl-benzofuran-3-yl)-acrylic acid ethyl ester (intermediate 62) were dissolved in EtOAc in the presence of Palladium on charcoal and Argon. To this was connected a H_2-balloon and hydrogenation was carried out for 12h. The palladium was filtered off and the solvents were evaporated affording pure title compound (80mg, 80%). HPLC: 3.53 min. LC-MS: M/Z ESI: 1.68 min, 247.25 (M+1).

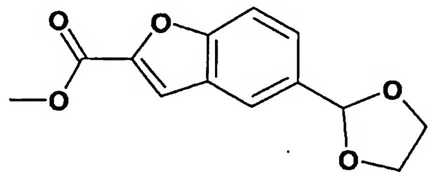
Intermediate 72: 2-Methyl-5-[1,3]dioxolan-2-yl-benzofuran



5-[1,3]Dioxolan-2-yl-benzofuran (50mg, 0.26mmol) was dissolved in THF (2 mL) and the solution was cooled down to –78°C. Butyl lithium (180uL, 1.1eq.) was added dropwise. This mixture was stirred 30 min at 25°C. Then the reaction mixture was cooled down to –78°C and iodomethane (18.1 uL, 1.1eq.) dissolved in 1 mL THF was added dropwise to the reaction mixture. The temperature was increased slowly to room temperature overnight. Despite some starting material was detected, water and ethyl acetate were added to the mixture and the aqueous layer was extracted 3 times. Combined organic phases was dried over $MgSO_4$, filtrated and evaporated to give 2-methyl-5-[1,3]dioxolan-2-yl-benzofuran (41.2 mg, 70%) sufficiently pure to be used in the next step.

LC-MS: M/Z ESI: 1.71 min, 205.34 (M+1).

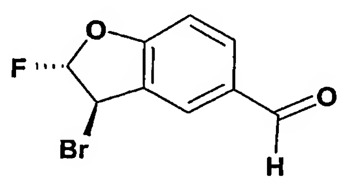
Intermediate 73: 5-[1,3]Dioxolan-2-yl-benzofuran-2-carboxylic acid methyl ester



5-[1,3]Dioxolan-2-yl-benzofuran (50mg, 0.26mmol) was dissolved in THF (2 mL) and the solution was cooled down to –78°C. Butyl lithium (180uL, 1.1eq.) was added dropwise. This mixture was stirred 30 min at 25°C. Then the reaction mixture was cooled down to –78°C and methyl cyanoformate (23 uL, 1.1eq.) dissolved in 1 mL THF was added dropwise to the reaction mixture. After 1h30 only small amount of starting material was detected and two major compounds were formed (expected product/dimer 73:27). The temperature was increased slowly to room temperature overnight. Water and ethyl acetate were added to the mixture and the aqueous layer was extracted 3 times. Combined organic phases was dried over $MgSO_4$, filtrated and evaporated to give the 5-[1,3]Dioxolan-2-yl-benzofuran-2-carboxylic acid methyl ester (31.9 mg, 44%) mixed with the dimer (expected product/dimer 46:54). The mixture was used directly in the next step.

LC-MS: M/Z ESI: 1.54 min, 249.26 (M+1) and 1.88 min, 407.20 (M+1, Dimer).

Intermediate 74: 3-Bromo-2-fluoro-benzofuran-5-carbaldehyde

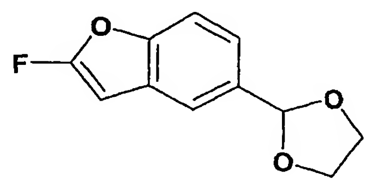


Benzofuran-5-carbaldehyde (100 mg, 0.68 mmol) in ether (1 mL) was added to a cold solution (-78°C) of NBS (158 mg, 1.3 eq) and pyridinium poly(hydrogen fluoride) 70% (0.850 mL) in ether (4 mL) in a polypropylene tube. The reaction was allowed to warm up to room temperature overnight. The reaction mixture was poured into ice water and extracted with ether. The ether phase was washed with aqueous bicarbonate, dried over

sodium sulfate, filtrated and evaporated to give 3-bromo-2-fluoro-benzofuran-5-carbaldehyde (141.6 mg). It was purified on reverse phase HPLC (solvents gradient H_2O/CH_3CN 0.1% TFA) affording the title compound (62 mg, 37%), which was used in the next step.

LC-MS: M/Z ESI: 1.56 min. HPLC=3.11 min (99.34%). ^{1}H NMR: (DMSO-d6) δ 9.94 (s, 1H), 8.09 (d, 1H, ^3J=1.8 Hz), 7.99 (dd, 1H, ^3J=8.4, 1.8 Hz), 7.38 (d, 1H, ^3J=8.4 Hz), 6.87 (d, 1H, $^2J_{H-F}$=59 Hz), 6.01 (d, 1H, $^3J_{H-F}$=15.1 Hz). ^{19}F NMR: (DMSO-d6) δ -114.80, -114.88.

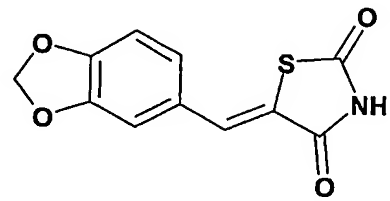
Intermediate 75: 2-Fluoro-5-[1,3]dioxolan-2-yl-benzofuran



5-[1,3]Dioxolan-2-yl-benzofuran (50mg, 0.26mmol) was dissolved in THF (2 mL) and the solution was cooled down to –78°C. Butyl lithium (180uL, 1.1eq.) was added dropwise. This mixture was stirred 30 min at 25°C. Then the reaction mixture was cooled down to –78°C and N-fluorodibenzenesulfonamide (91 mg, 1.1eq.), dissolved in 1 mL THF, was added dropwise to the reaction mixture. The mixture was stirred overnight between –78°C and room temperature. Water and ethyl acetate were added to the mixture and the aqueous layer was extracted 3 times. Combined organic phases was dried over $MgSO_4$, filtrated and evaporated, to give the 2-Fluoro-5-[1,3]dioxolan-2-yl-benzofuran (75 mg) mixed with side products. However it was sufficiently pure to be used for the next step.

The following examples have been synthesized:

Example 1: Preparation of 5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione



In a 100ml round bottom flask were placed 20g of thiazolidine, 15.6g of piperonal and 7.7g of beta-alanine in 80ml of acetic acid. The reaction was stirred for 3h at 100°C and then slowly cooled to room temperature, while the desired condensation product crystallized. The crystals were filtered, washed with acetic acid (rt.) and water than recrystallized from DME (25ml), affording 28g (84%) of pure 5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione. The corresponding potassium salt was obtained via the following route: 5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione was suspended in THF, followed by the addition of 1N solution of KOH in water (1.0 eq.). A clear solution has been obtained, which upon lyophilization gave pure potassium salt of 5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazolidine-2,4-dione.

HPLC: 3.48 min. LC-MS: M/Z ESI: 1.31 min, 248.12 (M-1). NMR (parent): ^1H NMR (DMSO-d6) δ 12.5 (br. s, 1H), 7.71 (s, 1H), 7.06-7.16 (m, 3H), 6.12 (s, 2H).

In cases were the final compounds did not crystallize from the reaction solutions, small quantities of water were added, leading to the precipitation of the desired condensation product.

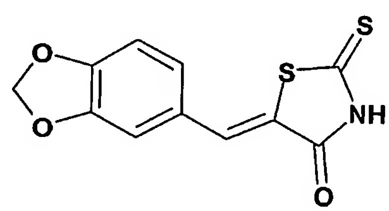
The crude either precipitated pure enough from the reaction mixture, or was recrystallized from an appropriate solvent like DME, methanol, EtOAc or purified by flash-chromatography using EtOAc, cyclohexane mixtures as eluents.

Alternativly the final compounds could be synthesized in a parallel manner according to the following protocol:

In a parallel synthesizer Quest 210™ was placed the corresponding aldehyde, to which was added a mixture of piperidine (17.9 mg/tube) and 2,4-thiazolidinedione (49.2 mg/tube) in

DME (2ml/tube). The reactions were stirred for 3h at 120°C and then cooled to room temperature under agitation. 2ml of H_2O were added. Those compounds, which precipitated were filtered off via the lower manifold. The remaining clear solutions were reduced in volume, followed by the addition of water. The so formed solids were filtered and washed with little amount of DME, affording pure condensation products.

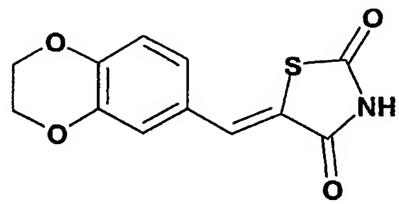
<u>Example 2: Preparation of 5-(1,3-benzodioxol-5-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one</u>



In a 24ml vial was placed 1g of commercially available rhodanine, 1.3g of piperonal and 0.5ml of TEA in 10ml of DME. The reaction was stirred for 5h at 120°C and then cooled to room temperature upon which the final product precipitated. The solid was filtered and washed with DME affording 1.6 g (80%) of orange powder.

LC-MS: M/Z ESI: 1.46 min, 266.00 (M+1), 264.08 (M-1). NMR (parent): ^1H NMR (DMSO-d6) δ 13.75 (br. s, 1H), 7.58 (s, 1H), 7.08-7.18 (m, 3H), 6.14 (s, 2H).

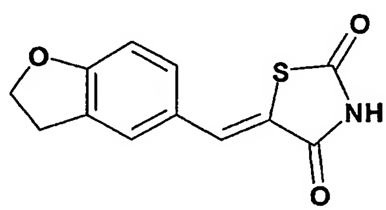
<u>Example 3: Preparation of 5-(2,3-dihydro-1,4-benzodioxin-6-ylmethylene)-1,3-thiazolidine-2,4-dione:</u>



Following the general method as outlined in Example 1, starting from 2,3-dihydro-1,4-benzodioxin-6-carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.58 min. LC-MS: M/Z ESI: 1.32 min, 262.16 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.52 (br. s, 1H), 7.68 (s, 1H,), 7.09 (dd, 2H, J = 1.9, 7.1), 7.00 (d, 1H, J = 9.0Hz), 4.36-4.22 (m, 4H).

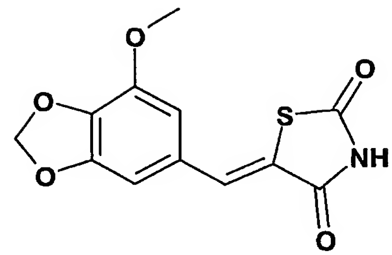
Example 4: Preparation of 5-(2,3-dihydro-1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione:



Following the general method as outlined in Example 1, starting from 2,3-dihydro-1-benzofuran-5-carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.27 min. LC-MS: M/Z ESI: 1.37 min, 246.18 (M-1). ^{1}H NMR: (DMSO-d6) δ 9.80 (br. s, 1H), 7.37 (s, 1H,), 7.25 (d, 1H, J = 8.3), 7.21 (s, 1H), 6.80 (d, 1H, J = 8.3Hz), 4.54 (t, 2H, J = 8.85), 3.19 (t, 2H, J = 8.85)

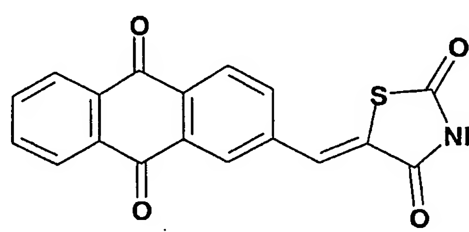
Example 5: Preparation of 5-[(7-methoxy-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 7-methoxy-1,3-benzodioxol-5-yl)carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.57 min. LC-MS: M/Z ESI: 1.30 min, 278.07 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.63 (br. s, 1H), 7.78 (s, 1H,), 7.65 (s, 1H), 7.57 (d, 1H, J = 8.5Hz), 7.45 (dd, 2H, J = 0.8, 7.6).

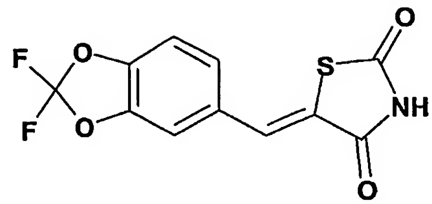
Example 6: Preparation of 5-[(9,10-dioxo-9,10-dihydroanthracen-2-yl)methylene]-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from (9,10-dioxo-9,10-dihydroanthracen-2-yl)carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 4.12 min. LC-MS: M/Z ESI: 1.50 min, 334.09 (M-1).

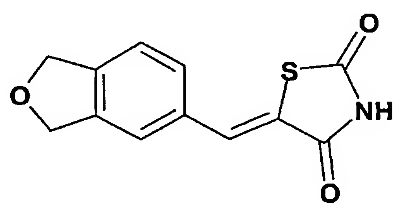
Example 7: Preparation of (5-[(2,2-difluoro-1,3-benzodioxol-5-yl)methylene]-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from (2,2-difluoro-1,3-benzodioxol-5-yl)carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.85 min. LC-MS (10 min.): M/Z ESI: 3.15 min, 284.11 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.63 (br. s, 1H), 7.78 (s, 1H,), 7.65 (s, 1H), 7.57 (d, 1H, J = 8.5Hz), 7.45 (dd, 2H, J = 0.8, 7.6)

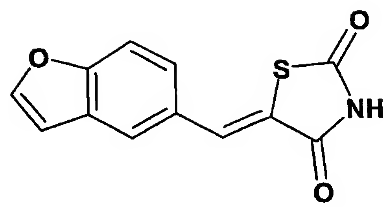
Example 8: Preparation of 5-(1,3-dihydro-2-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 1,3-dihydro-2-benzofuran-5-carbaldehyde (intermediate 4) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.89 min. LC-MS: M/Z ESI: 1.20 min, 246.20 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.60 (br. s, 1H), 7.80 (s, 1H,), 7.56-7.42 (m, 2H), 5.03 (s, 4H)

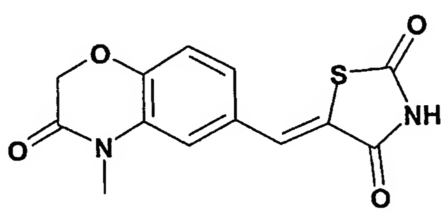
Example 9: Preparation of 5-(1-benzofuran-5-ylmethylene)-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 1-benzofuran-5-carbaldehyde (intermediate 1) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.54 min. LC-MS: M/Z ESI: 1.47 min, 244.20 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.10 (d, 1H, J = 2.2Hz), 7.92 (s, 2H), 7.74 (d, 1H, J = 8.6Hz), 7.57 (d, 1H, J = 8.6Hz), 7.07 (s, 1H)

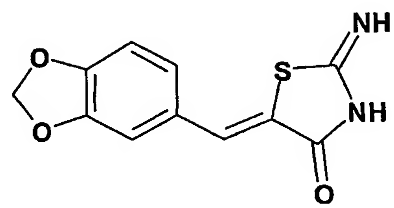
Example 10: Preparation of 5-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methylene]-1,3-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from [(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)carbaldehyde (intermediate 2) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.79 min. LC-MS: M/Z ESI: 1.19 min, 289.22 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.81 (s, 1H), 7.41 (s, 1H), 7.13-7.26 (d, 2H), 4.74 (s, 2H), 2.99 (s, 3H)

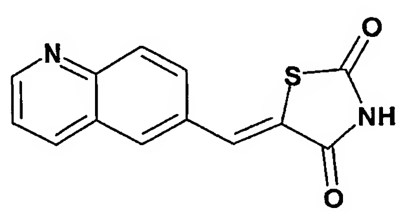
Example 11: Preparation of 5-(1,3-benzodioxol-5-ylmethylene)-2-imino-1,3-thiazolidine-4-one



Following the general method as outlined in Example 1, starting from 1,3-benzodioxol-5-carbaldehyde and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.

HPLC: 2.29 min. LC-MS: M/Z ESI: 1.21 min, 247.25 (M-1).

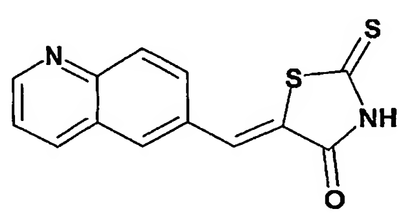
Example 12: Preparation of 5-Quinolin-6-ylmethylene-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from quinoline-6-carbaldehyde (intermediate 5) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

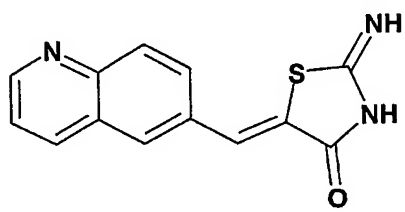
HPLC: 1.445 min. LC-MS: M/Z ESI: 1.17 min, 257.21 (M+1). ^{1}H NMR: (DMSO-d6) δ 8.88 (d, J=6Hz, 1H), 8.40 (d, J=9Hz, 1H), 8.07-7.90 (m, 3H), 7.55 (q, J=6Hz, 9Hz, 1H), 7.45 (s, 1H).

Example 13: 5-Quinolin-6-ylmethylene-2-thioxo-thiazolidin-4-one



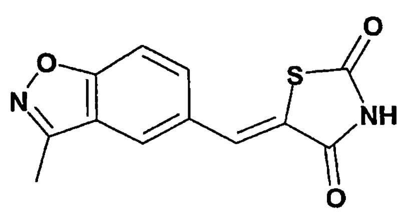
Following the general method as outlined in Example 1, starting from quinoline-6-carbaldehyde (intermediate 5) and rhodanine, the title compound was obtained.
HPLC: 2.05 min. LC-MS: M/Z ESI: 1.25 min, 273.14 (M+1). ^{1}H NMR: (DMSO-d6) δ 14.00 (br. s, 1H), 8.97 (d, J=2.3Hz, 1H), 8.23 (d, J=9Hz, 1H), 8.10 (d, J=9Hz, 1H), 7.95 (d, J=9Hz, 1H), 7.79 (s, 1H), 7.61 (q, J=3Hz, 9Hz, 1H).

Example 14: 2-Imino-5-quinolin-6-ylmethylene-thiazolidin-4-one



Following the general method as outlined in Example 1, starting from quinoline-6-carbaldehyde (intermediate 5) and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.
HPLC: 1.16 min. LC-MS: M/Z ESI: 1.10 min, 256.18 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.84 (s, 1H), 8.37 (d, J=6Hz, 1H), 8.02-7.86 (m, 3H), 7.52 (q, J=6Hz, 9Hz, 1H), 7.26 (s, 1H), 7.02 (b. s, 1H).

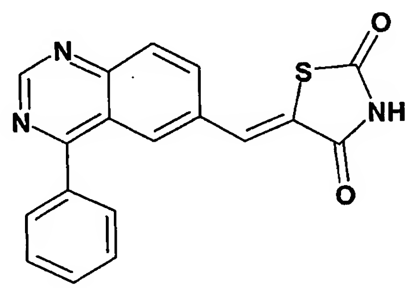
Example 15: 5-(3-Methyl-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Methyl-benzo[d]isoxazole-5-carbaldehyde (intermediate 6) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

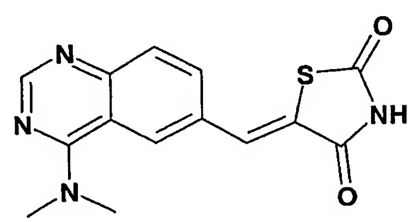
HPLC: 2.99 min. LC-MS: M/Z ESI: 1.30 min, 259.17 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.85 (s, 2H), 2.59 (s, 3H).

Example 16: 5-(4-Phenyl-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 4-Phenyl-quinazoline-6-carbaldehyde (intermediate 13) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.
HPLC: 3.45 min. LC-MS: M/Z ESI: 1.25 min, 334.15 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.74 (br. s, 1H), 9.43 (s, 1H), 8.24 (m, 2H), 8.00-7.86 (m, 2H), 7.72-7.66 (m, 5H).

Example 17: 5-(4-Dimethylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione



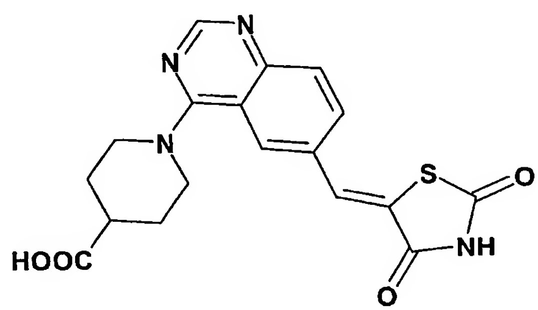
Following the general method as outlined in Example 1, starting from 4-Dimethylamino-quinazoline-6-carbaldehyde (intermediate 14) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.
HPLC: 1.47 min. LC-MS: M/Z ESI: 1.26 min, 301.26 (M+1). ^{1}H NMR: (DMSO-d6) δ 8.81 (s, 1H), 8.54 (s, 1H), 8.16-7.95 (m, 3H), 7.13-7.26 (d, 2H), 3.63 (s, 6H).

The following examples were synthesized as desribed in Example 1 and 17 starting from intermediates 15 to 31 and 1,3-thiazolidine-2,4-dione

Example	Intermediate# as starting material	Compound name	Mass (M+1)
18	16	5-[(4-aminoquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione	273.29
19	15	5-[(4-piperidin-1-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione	341.40
20	22	5-[(4-morpholin-4-ylquinazolin-6-yl)methylene]-1,3-thiazolidine-2,4-dione	343.20
21	17	5-{[4-(benzylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	363.10
22	21	5-{[4-(diethylamino)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	329.30
23	18	5-({4-[(pyridin-2-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione	364.40
24	19	5-({4-[(pyridin-3-ylmethyl)amino]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione	364.40
25	23	ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-3-carboxylate	413.20
26	25	ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-4-carboxylate	413.30
27	24	tert-butyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}-L-prolinate	427.20
28	20	5-{[4-(4-methylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	356.13
29	31	5-{[4-(4-pyrimidin-2-ylpiperazin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	420.20

30	30	5-({4-[4-(4-fluorophenyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione	435.30
31	29	5-{[4-(4-benzylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	431.30
32	28	5-({4-[4-(2-phenylethyl)piperidin-1-yl]quinazolin-6-yl}methylene)-1,3-thiazolidine-2,4-dione	445.40
33	27	5-{[4-(4-methylpiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	355.20
34	26	5-{[4-(4-hydroxypiperidin-1-yl)quinazolin-6-yl]methylene}-1,3-thiazolidine-2,4-dione	357.40

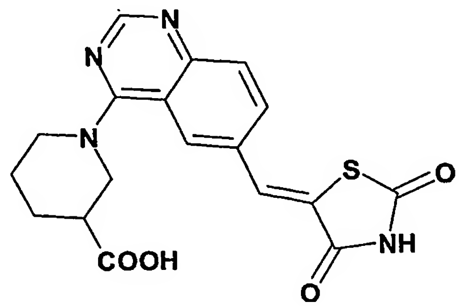
Example 35: 1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-4-carboxylic acid



50 mg of Ethyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}piperidine-4-carboxylate (example 26) was dissolved in 2ml solution of THF/water (1/1). A few drops of 5N NaOH were added, and the reaction was stirred for 12h at rt. After completion of the reaction, solvents were evaporated and titled compound was precipitated in diethylether as a yellow solid (40mg, 82%).

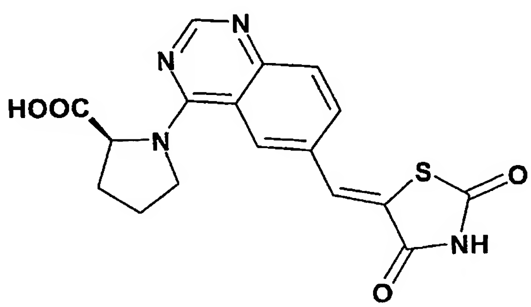
HPLC: 1.43 min. LC-MS: M/Z ESI: 1.15 min, 385.20 (M+1).

Example 36: 1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-piperidine-3-carboxylic acid



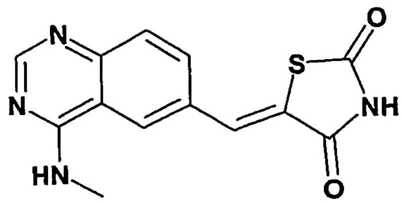
Following the general method as outlined in Example 35, the title compound was obtained. HPLC:1.50 min. LC-MS: M/Z ESI: 1.10 min, 385.40 (M+1).

Example 37: 1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-pyrrolidine-2-carboxylic acid



10 mg of tert-butyl 1-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]quinazolin-4-yl}-L-prolinate (example 27) was stirred in a 25% (TFA/DCM) solution for 12h at rt. The solvents were evaporated under vacuo and expected compound was precipitated with dietyl ether to give pure 1-[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-quinazolin-4-yl]-pyrrolidine-2-carboxylic acid (7 mg, 81%).
HPLC: 1.43 min. LC-MS: M/Z ESI: 1.10 min, 371.30 (M+1).

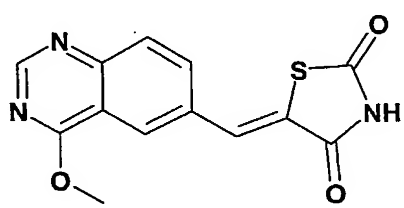
Example 38: 5-(4-Methylamino-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 4-methylamino-quinazoline-6-carbaldehyde (intermediate 11) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 1.43 min. LC-MS: M/Z ESI: 1.03 min, 287.19 (M+1). ^{1}H NMR: (DMSO-d6) δ 11.97 (br. s, 1H), 8.53 (br. s, 2H), 8.37 (s, 1H), 7.92 (d, J=8Hz, 1H), 7.76 (s, 2H), 3.03 (s, 3H)

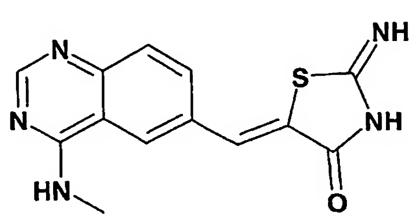
Example 39: 5-(4-Methoxy-quinazolin-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example. 1, starting from 4-methoxy-quinazoline-6-carbaldehyde (intermediate 10) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

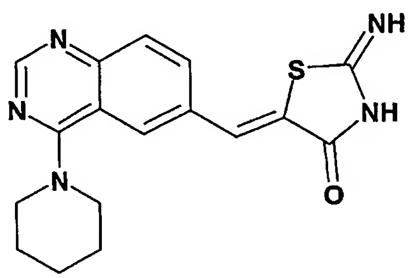
HPLC: 2.57 min. LC-MS: M/Z ESI: 1.12 min, 288.20 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.74 (br. s, 1H), 8.86 (s, 1H), 8.32 (s, 1H), 8.11 (m, 1H), 8.03-7.98 (m, 2H), 4.18 (s, 3H)

Example 40: 2-Imino-5-(4-methylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one



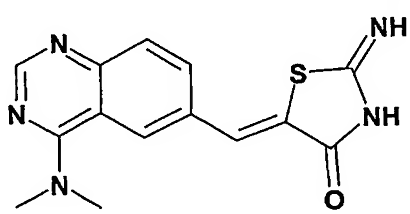
Following the general method as outlined in Example 1, starting from 4-methylamino-quinazoline-6-carbaldehyde (intermediate 11) and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.
HPLC: 2.43 min. LC-MS: M/Z ESI: 1.07 min, 286.14 (M+1).

Example 41: 2-Imino-5-(4-piperidine-quinazolin-6-ylmethylene)-thiazolidin-4-one



Following the general method as outlined in Example 1, starting from 4-piperidine-quinazoline-6-carbaldehyde (intermediate 72) and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.
HPLC: 1.78 min. LC-MS: M/Z ESI: 1.40 min, 340.26 (M+1). ^{1}H NMR: (DMSO-d6) δ 8.76 (s, 1H), 8.18 (s, 1H), 8.16 (d, J=6Hz, 1H), 7.88 (d, J=9Hz, 1H), 7.80 (s, 1H), 4.09 (s, 4H), 1.80 (s, 6H).

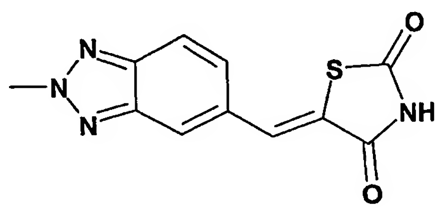
Example 42: 2-Imino-5-(4-dimethylamino-quinazolin-6-ylmethylene)-thiazolidin-4-one



Following the general method as outlined in Example 1, starting from 4-piperidine-quinazoline-6-carbaldehyde (intermediate 14) and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.

HPLC: 1.32 min. LC-MS(10 min.): M/Z ESI: 1.54 min, 300.23 (M+1). ^{1}H NMR: (DMSO-d6) δ 8.82 (s, 1H), 8.53 (s, 1H), 8.16 (d, J=9Hz, 1H), 7.87 (t, J=9Hz, 2H), 3.65 (s, 6H).

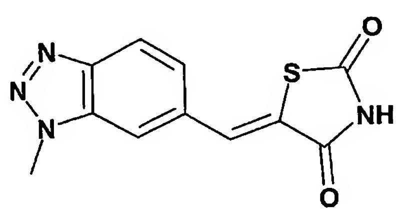
Example 43: 5-(2-Methyl-2H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 2-Methyl-2H-benzotrizaole-5-carbaldehyde (intermediate 33) and thiazolidindione, the title compound was obtained.

HPLC: 2.68 min. ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.98 (s, 1H), 7.92 (d, J=9Hz, 1H), 7.62 (d, J=6Hz, 1H), 7.43 (s, 1H), 4.48 (s, 3H).

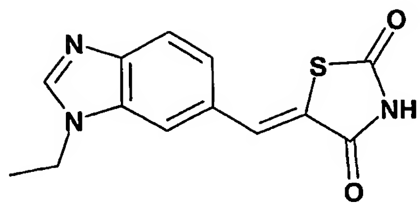
Example 44: 5-(3-Methyl-3H-benzotriazol-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Methyl-3H-benzotrizaole-5-carbaldehyde (intermediate 34) and thiazolidindione, the title compound was obtained.

HPLC: 2.35 min. LC-MS: M/Z ESI: 1.22 min, 259.23 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.17 (d, J=9Hz, 1H), 8.07 (s, 1H), 7.62 (d, J=6Hz, 1H), 7.47 (s, 1H), 4.33 (s, 3H).

Example 45: 5-(3-Ethyl-3H-benzimidazol-5-ylmethylene)-thiazolidine-2,4-dione



5-(4-Amino-3-ethylamino-benzylidene)-thiazolidine-2,4-dione (50mg, 0.19mmol) (intermediate 36) was dissolved in formic acid (5mL) and the solution stirred at 100°C over night. Formic acid was then removed *in vacuo*. The crude residue was then purified by silica gel column to give the title compound (35mg, 63%).

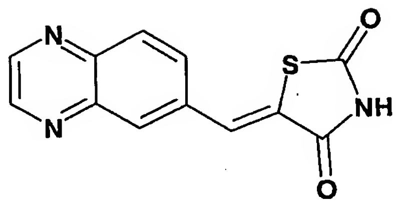
HPLC: 1.71 min. LC-MS: M/Z ESI: 0.82 min, 274.21 (M+1).

The following examples were synthesized as desribed in Example 45 starting from intermediates 37 to 54 and 1,3-thiazolidine-2,4-dione.

Example	Intermediate# as starting material	Compound name	Mass (M+1)
46	37	5-{[1-(4-phenylbutyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione	378.30
47	50	5-[(1-prop-2-yn-1-yl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione	284.24
48	38	5-[(1-{2-[4-(trifluoromethyl)phenyl]ethyl}-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione	418.17
49	39	5-({1-[2-(4-hydroxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	366.26
50	40	methyl 4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylate	386.35
51	41	5-({1-[2-(5-methoxy-1H-indol-3-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	419.21

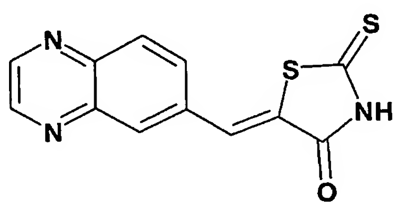
52	42	5-({1-[(1-methyl-1H-pyrazol-4-yl)methyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	340.99
53	43	5-({1-[2-(3,4-dimethoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	410.37
54	54	5-({1-[2-(4-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	442.51
55	44	5-({1-[4-(trifluoromethyl)benzyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	404.16
56	45	4-{6-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1H-benzimidazol-1-yl}cyclohexanecarboxylic acid	372.18
57	46	5-[(1-isobutyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione	302.25
58	47	5-({1-[2-(1,3-benzodioxol-4-yl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	394.27
59	48	5-({1-[2-(2-phenoxyphenyl)ethyl]-1H-benzimidazol-6-yl}methylene)-1,3-thiazolidine-2,4-dione	442.29
60	49	5-{[1-(3,3-diphenylpropyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione	440.27
61	51	5-{[1-(2-methoxybenzyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione	366.33
62	52	5-{[1-(3-furylmethyl)-1H-benzimidazol-6-yl]methylene}-1,3-thiazolidine-2,4-dione	326.24
63	53	5-[(1-propyl-1H-benzimidazol-6-yl)methylene]-1,3-thiazolidine-2,4-dione	288.18

Example 64: 5-Quinoxalin-6-ylmethylene-thiazolidine-2,4-dione



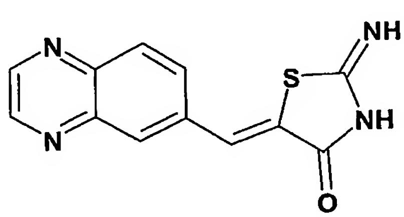
Following the general method as outlined in Example 1, starting from quinoxaline-6-carbaldehyde (intermediate 55) and thiazolidindione, the title compound was obtained. HPLC: 2.48 min. LC-MS: M/Z ESI: 1.01 min, 256.20 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.93 (d, J=9Hz, 2H), 8.18 (s, 1H), 8.10 (d, J=9Hz, 1H), 8.03 (d, J=9Hz, 1H), 7.51 (s, 1H).

Example 65: 5-Quinoxalin-6-ylmethylene-2-thioxo-thiazolidin-4-one



Following the general method as outlined in Example 1, starting from quinoxaline-6-carbaldehyde (intermediate 55) and rhodanine, the title compound was obtained. HPLC: 3.10 min. LC-MS: M/Z ESI: 1.17 min, 272.13 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.00 (br. s, 1H), 9.02 (s, 2H), 8.31 (s, 1H), 8.21 (d, J=9Hz, 1H), 8.04 (d, J=9Hz, 1H), 7.90 (s, 1H)

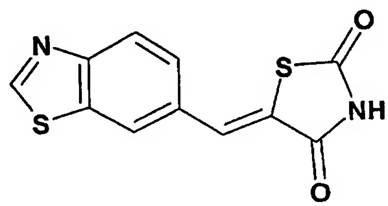
Example 66: 2-Imino-5-quinoxalin-6-ylmethylene-thiazolidin-4-one



Following the general method as outlined in Example 1, starting from quinoxaline-6-carbaldehyde (intermediate 55) and 2-imino-1,3-thiazolidin-4-one, the title compound was obtained.

HPLC: 1.97 min. LC-MS: M/Z ESI: 1.02 min, 255.19 (M-1). ^{1}H NMR: (DMSO-d6) δ 9.57-9.30 (b. d, J=81Hz, 2H), 9.00 (s, 2H), 8.26-8.07 (m, 3H), 7.84 (s, 1H).

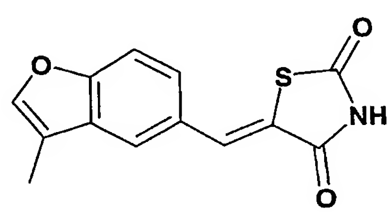
Example 67: 5-Benzothiazol-6-ylmethylene-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from quinoxaline-6-carbaldehyde (intermediate 56) and thiazolidindione, the title compound was obtained.

HPLC: 2.85 min. LC-MS: M/Z ESI: 1.06 min, 261.11 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 9.39 (s, 1H), 8.27 (s, 1H), 8.11 (d, J=9Hz, 1H), 7.70 (d, J=9Hz, 1H), 7.42 (s, 1H).

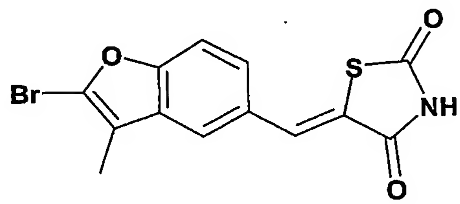
Example 68: 5-(3-Methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Methyl-benzofuran-5-carbaldehyde (intermediate 57) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 1.47 min. LC-MS: M/Z ESI: 1.15 min, 257.21 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.50 (br. s, 1H), 8.87 (d, *J*=6Hz, 1H), 8.38 (d, *J*=9Hz, 1H), 8.07 (t, *J*=12Hz, 2H), 7.92 (d, *J*=9Hz, 1H), 7.53 (q, *J*=6Hz, 12Hz, 1H), 7.45 (s, 1H).

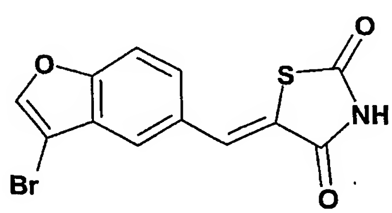
Example 69: 5-(2-Bromo-3-methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione



In a 25 ml 3 neck flask was placed 5-(3-methyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione (100mg, 0.39mmol) (example 68) and Br2 (20 ul, 1eq.) in 2 ml of AcOH at 0°C. The mixture was allowed to warm to room temperature. After 2h at room temperature another equivalent of Br_2 was added. After 3h the reaction was filtered off to obtain a yellow product being the title compound (87mg, 66%).

LC-MS: M/Z ESI: 1.69 min, 339.8 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.50 (br. s, 1H), 7.93 (s, 1H), 7.82 (s, 1H), 7.72 (d, *J*=6Hz, 1H), 7.54 (d, *J*=6Hz, 1H), 2.20 (s, 3H).

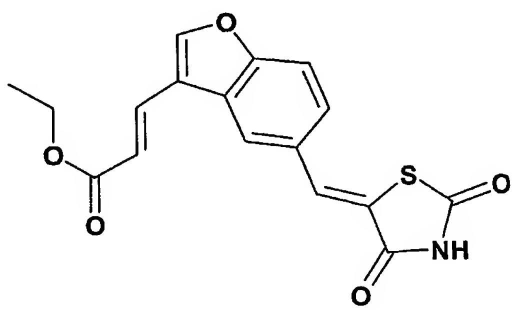
Example 70: 5-(3-bromo-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Bromo-benzofuran-5-carbaldehyde (intermediate 58) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.92 min. LC-MS: M/Z ESI: 1.57 min, 325.17 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.60 (br. s, 1H), 8.42 (s, 1H), 8.00 (s, 1H), 7.85 (d, J=23Hz, 1H), 7.76 (s, 1H), 7.63 (d, J=23Hz, 1H).

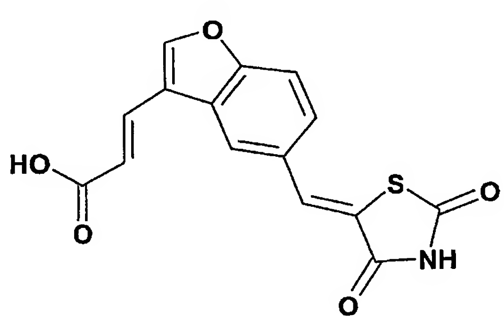
Example 71: 3 -[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid ethyl ester



Following the general method as outlined in Example 1, starting from 3-(5-Formyl-benzofuran-3-yl)-acrylic acid ethyl ester (intermediate 60) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 4.00min. LC-MS: M/Z ESI: 1.60 min, 342.20 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.50 (br. s, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 8.08 (s, 1H), 7.83 (m, 2H), 7.62 (s, 1H), 4.22 (q, J=6Hz, 9Hz, 2H), 1.28 (t, J=9Hz, 3H).

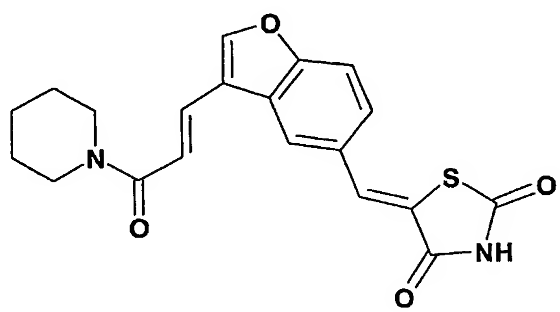
Example 72: 3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid



3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid ethyl ester (205mg, 0.6mmol) (example 71) were dissolved in THF/water 4:2. To this solution was added under stirring 81mg (4eq.) of $LiOH.H_2O$. The reaction was stirred for 15h. The solvents were evaporated, and the residue was precipitated with ether. The solid was washed with 1NHCl and dried to afford 170mg (90%) of pure 3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid.

HPLC: 3.25 min. LC-MS: M/Z ESI: 1.01 min, 314.11 (M-1). ^{1}H NMR: (DMSO-d6) δ 8.22 (s, 1H), 8.03 (s, 1H), 7.58 (dd, J=9Hz, 33Hz, 2H), 7.43 (s, 1H), 7.25 (d, J=18 Hz, 1H), 7.07 (s, 1H).

Example 73: 5 -[3-(3-Oxo-3-piperidin-1-yl-propenyl)-benzofuran-5-ylmethylene]-thiazolidine-2,4-dione



180 mg (0.57mmol) of 3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-acrylic acid (example 72) was suspended in THF (25ml). To this suspension was added DIEA (2eq.) and piperidine (3eq.). Under stirring was added PyBOP (1.5 eq.). After 30min the reaction mixture became clear, after an additional 1h a precipitate was formed. The reaction was stirred overnight. The precipitate was filtered off and washed with THF and 1N HCl affording the title compound in high purity.

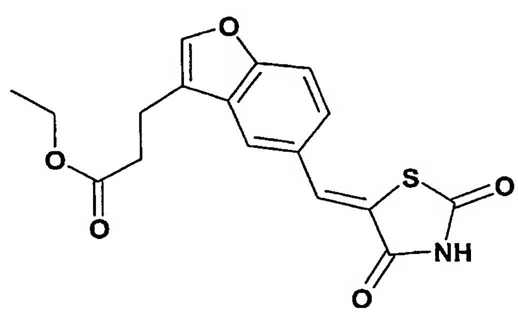
HPLC: 3.91 min. LC-MS: M/Z ESI: 1.58 min, 383.22 (M+1). ^{1}H NMR: (DMSO-d6) δ 8.46 (s, 1H), 8.19 (s, 1H), 7.71-7.51 (m, 4H), 7.23 (d, J=15Hz, 1H), 3.73 (d, J=48Hz, 2H), 1.51 (d, J=36Hz, 3H).

The following amides were synthesized according to the synthesis of example 73.

Example	Amine as starting material	Compound name	Mass (M+1)
74	Proline-methylester	Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)prolinate	427.15
75	D-proline-methylester	Methyl 1-((3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-D-prolinate	413.15
76	Pyrollidine	(5-({3-[(3-oxo-3-pyrrolidin-1-ylprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	369.52
77	Morpholine	5-({3-[3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	385.07
78	L-proline-methylester	Methyl 1-(3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}prop-2-enoyl)-L-prolinate	427.13
79	N-methyl-cyclohexylamine	N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-methylacrylamide	411.12
80	N-ethyl-hydroxyethyl-amine	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-ethyl-N-(2-hydroxyethyl)acrylamide	387.10
81	Cyclobutylamine	N-cyclobutyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide	369.13
82	Azetidine	5-({3-[3-azetidin-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	355.64
83	1,3-dihydro-2H-isoindole	5-({3-[3-(1,3-dihydro-2H-isoindol-2-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	415.00 (M-1)
84	Azepan	5-({3-[3-azepan-1-yl-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	397.46

85	Piperidin-1-ylamine	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-piperidin-1-ylacrylamide	398.00
86	Pyridin-3-yl-methylamine	3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}-N-(pyridin-3-ylmethyl)acrylamide	406.10
87	Cyclohexylamine	N-cyclohexyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide	397.08
88	4-N-methyl-piperazine	5-({3-[3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	398.02
89	Cycloheptylamine	N-cycloheptyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide	411.44
90	Pyroline	5-({3-[3-(2,5-dihydro-1H-pyrrol-1-yl)-3-oxoprop-1-en-1-yl]-1-benzofuran-5-yl}methylene)-1,3-thiazolidine-2,4-dione	367.11
91	Cyclopentylamine	N-cyclopentyl-3-{5-[(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-1-benzofuran-3-yl}acrylamide	383.11

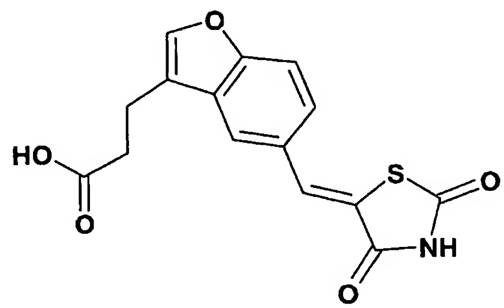
Example 92: 3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid ethyl ester



Following the general method as outlined in Example 1, starting from 3-(5-Formyl-benzofuran-3-yl)-propionic acid ethylester (intermediate 71) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.94mn. LC-MS: M/Z ESI: 2.87min, 346.15 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.92 (d, J=6Hz, 3H), 7.72 (d, J=9Hz, 1H), 7.53 (d, J=9Hz, 1H), 4.03 (q, J=9Hz, 15Hz, 2H), 2.94 (t, J=9Hz, 2H), 2.73 (t, J=6Hz, 2H), 1.14 (t, J=6Hz).

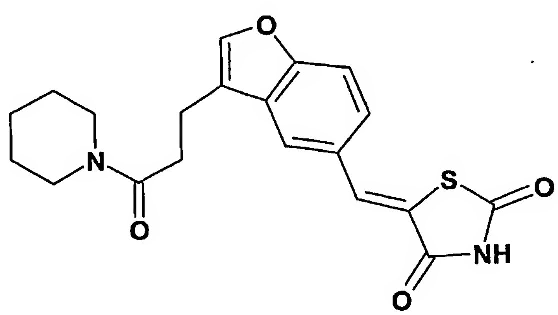
Example 93: 3-[5-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzofuran-3-yl]-propionic acid



The title compound was obtained applying standard saponifications techniques as described for example 72 using example 92 as starting material.

HPLC: 3.09 min. LC-MS(10 min.): M/Z ESI: 1.19min, 316.14 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 12.22 (b. s, 1H), 7.93 (d, J=12Hz, 3H), 7.70 (d, J=9Hz, 1H), 7.54 (d, J=9Hz, 1H), 2.91 (t, J=9Hz, 2H), 2.65 (t, 6Hz, 2H).

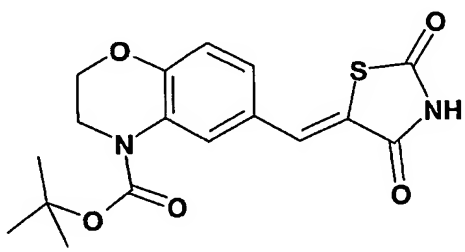
Example 94: 5-[3-(3-Oxo-3-piperidin-1-yl-propyl)-benzofuran-5-ylmethylene]-thiazolidine-2,4-dione



The title compound was obtained applying the synthetic protocol as described for example 73 using example 93 as starting material.

HPLC: 3.783 min. LC-MS: M/Z ESI: 1.46 min, 385.14 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.66 (br. s, 1H), 8.06 (s, 3H), 8.01 (s, 1H), 7.79 (s, 1H), 3.50-1.60 (m, 14H).

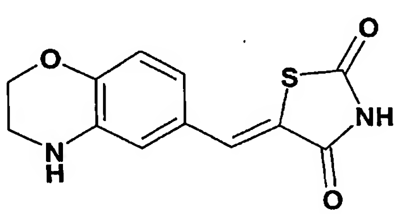
Example 95: 6 -(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester



Following the general method as outlined in Example 1, starting from 6-Formyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester (intermediate 62) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.52 min. LC-MS: M/Z ESI: min, 261.21 (M-Boc-1).

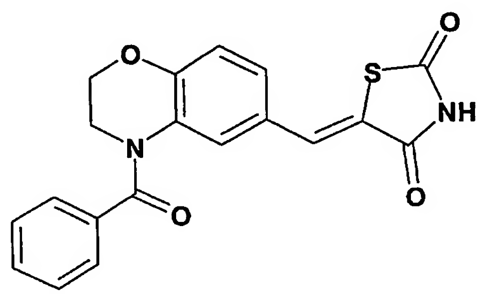
Example 96: 5-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione



100mg of 6-Formyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester (intermediate 62) were treated with TFA/DCM 25% for 2h. The solvents were evaporated to dryness and the remaining crude was used for the Knoevenagel reaction as outlined in Example 1 without further purification to obtain the title compound as yellow solid.

HPLC: 2.56 min. LC-MS: M/Z ESI: 1.14 min, 261.24 (M-1). [1]H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.57 (s, 1H), 6.78 (s, 3H), 4.17 (t, J=3Hz, 2H), 3.28 (t, J=6Hz, 2H).

Example 97: 5 -(4-Benzoyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione

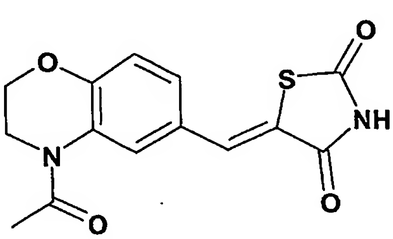


5-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione (example 96) (35mg, 0.13mmol) in 4ml anhydrous THF were treated with benzoylchloride (156uL, 10eq.) in the presence of DIEA (2eq.) for 3h. Excess of benzoylchloride was hydrolysed, EtOAc was added and the organic phase was washed with $NaHCO_3$ and brine. The crude was purified on silica gel using EtOAc/cyclohexane 3:7 as eluent affording 14mg (35%) of the title compound.

HPLC: 4.57 min. LC-MS: M/Z ESI: 2.11 min, 364.91 (M-1).

The following example was synthesized in the same way as described for example 97.

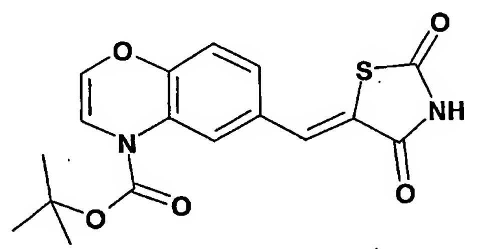
Example 98: 5-(4-Acetyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione



Yield = 43mg (95%)

HPLC: 2.65 min. LC-MS: M/Z ESI: 1.12 min, 305.24 (M+1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.30 (b s, 1H), 7.71 (s, 1H), 7.35 (d, J=9Hz, 1H), 7.05 (d, J=9Hz, 1H), 4.33 (t, J=6Hz, 2H), 4.00 (t, J=6Hz, 2H).

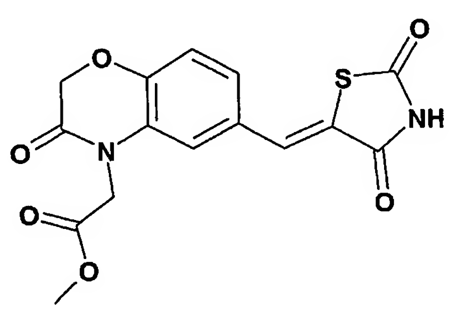
Example 99: 6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester



Following the general method as outlined in Example 1, starting from 6-Formyl-benzo[1,4]oxazine-4-carboxylic acid tert-butyl ester (intermediate 63) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 4.23 min. LC-MS: M/Z ESI: 1.82 min, 359.16 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.50 (br. s, 1H), 7.63 (d, J=3Hz, 2H), 7.31 (d, J=3Hz, 1H), 6.95 (d, J=6Hz, 1H), 6.30 (s, 2H).

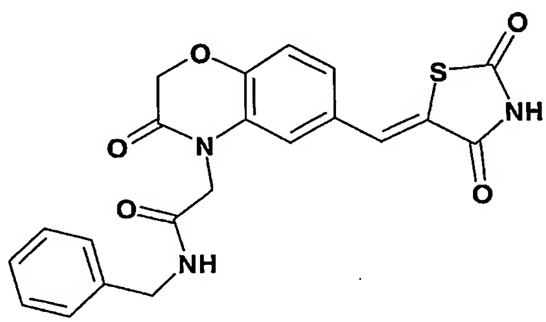
Example 100: [6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-acetic acid methyl ester



Following the general method as outlined in Example 1, starting from (6-Formyl-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-acetic acid methyl ester (intermediate 64) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.83 min. LC-MS: M/Z ESI: 1.20 min, 347.25 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.76 (s, 1H), 7.36 (s, 1H), 7.20 (m, 2H), 4.82 (d, J=15Hz, 4H), 3.71 (s, 3H).

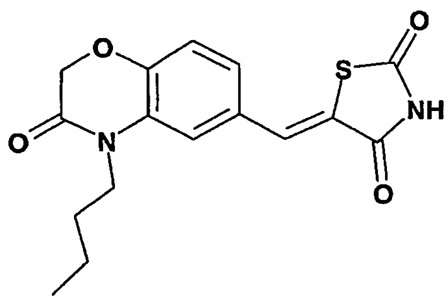
Example 101: N -Benzyl-2-[6-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetamide



[6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-acetic acid methyl ester (195mg, 0.56mmol) (example 100) were saponified using 2 eq. of LiOH as described for example 74 affording [6-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetic acid. The so obtained acid (50mg, 0.15mmol) was dissolved in THF. HOBt (32mg, 1.5eq.), EDC (43mg, 1.5eq.) and benzylamine (25mg, 1.5 eq.) were added while stirring. The reaction mixture was stirred for 15h at rt. EtOAc was added and the organic phase was washed with 1N HCl, $NaHCO_3$, brine each of which three times. The crude residue after evaporating the solvents was purified on silica gel using DCM/EtOAc as eluents to give the title compound as colourless powder (35mg, 54%).

HPLC: 3.06 min. LC-MS: M/Z ESI: 1.27 min, 424.21 (M+1).

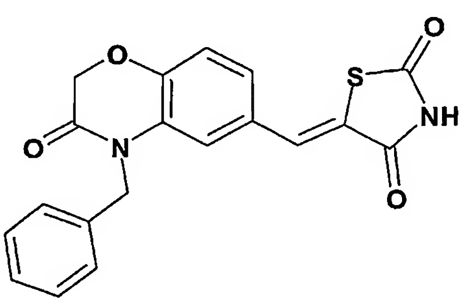
Example 102: 5-(4-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 4-Butyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde (intermediate 65) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.67 min. LC-MS: M/Z ESI: 1.49 min, 331.23 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.85 (s, 1H), 7.43 (s, 1H), 7.24 (d, J=6Hz, 1H), 7.15 (d, J=9Hz, 1H), 4.73 (s, 2H), 3.91 (t, J=3Hz, 2H), 1.57, (m, 2H), 1.36 (m, 2H), 0.91 (t, J=9Hz, 3H).

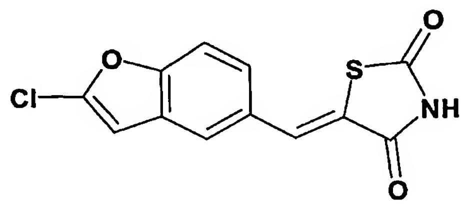
Example 103: 5-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-carbaldehyde (intermediate 66) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.67 min. LC-MS: M/Z ESI: 1.46 min, 365.17 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 7.68 (s, 1H), 7.38-7.22 (m, 8H), 5.24 (s, 2H), 4.97 (s, 2H).

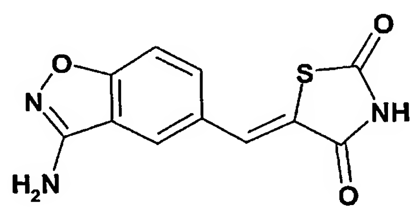
Example 104: 5-(2-Chloro-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 2-Chloro-5-[1,3]dioxolan-2-yl-benzofurane (intermediate 67) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.84 min. LC-MS: M/Z ESI: 1.62 min, 278.12 (M-1). ^{1}H NMR: (DMSO-d6) δ 7.90-7.75 (M, 2H), 7.68 (d, j=9Hz, 1H), 7.52 (d, J=9Hz, 1H), 7.09 (s, 1H).

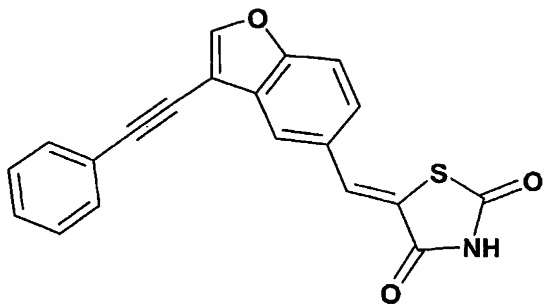
Example 105: 5-(3-Amino-benzo[d]isoxazol-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Amino-benzo[d]isoxazole-5-carbaldehyde (intermediate 68) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 2.45 min. LC-MS: M/Z ESI: 0.97 min, 260.17 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.60 (br. s, 1H), 8.01 (s, 1H), 7.85 (s, 1H), 7.60 (d, J=9Hz, 1H), 6.67 (s, 1H).

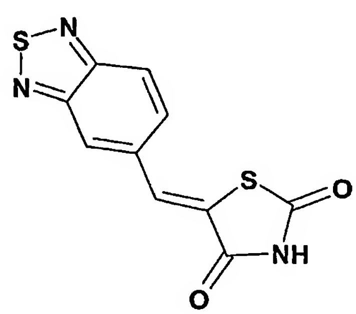
Example 106: 5-(3-Phenylethynyl-benzofuran-5-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 3-Phenylethynyl-benzofuran-5-carbaldehyde (intermediate 59) and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 4.82 min. LC-MS: M/Z ESI: 2.02 min, 344.18 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.49 (s, 1H), 7.92 (s, 1H), 7.72 (d, J=9Hz, 1H), 7.62 (m, 3H), 7.45 (m, 4H).

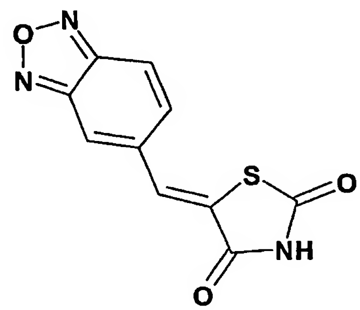
Example 107: 5-Benzo[1,2,5]thiadiazol-5-ylmethylene-thiazolidine-2,4-ione



Following the general method as outlined in Example 1, starting from 2,1,3-Benzothiadiazole-5-carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.03 min. LC-MS: M/Z ESI: 1.14 min, 262.11 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.11 (m, 2H), 7.90 (d, J=9Hz, 1H), 7.47 (s, 1H).

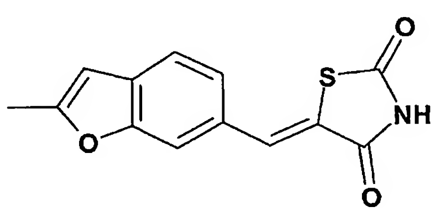
Example 108: 5-Benzo[1,2,5]oxadiazol-5-ylmethylene-thiazolidine-2,4-ione



Following the general method as outlined in Example 1, starting from 2,1,3-Benzoxadiazole-5-carbaldehyde and 1,3-thiazolidine-2,4-dione, the title compound was obtained.

HPLC: 3.02 min. LC-MS: M/Z ESI: 1.17 min, 246.17 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.58 (br. s, 1H), 8.07 (m, 2H), 7.82 (d, J=9Hz, 1H), 7.40 (s, 1H).

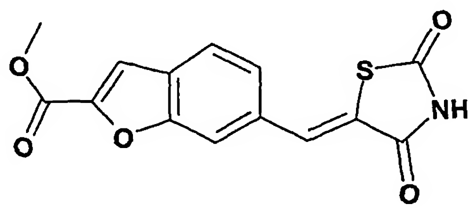
Example 109: 5-(2-Methyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 2-Methyl-5-[1,3]dioxolan-2-yl-benzofuran (intermediate 72) and 1,3-thiazolidine-2,4-dione, the title compound was obtained after purification on reverse phase HPLC (solvents gradient H_2O/CH_3CN 0.1% TFA).

HPLC: 3.65 min, 90.75%. LC-MS: M/Z ESI: 1.65 min, 258.21 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.45 (sl, 1H), 7.88 (s, 1H), 7.77 (d, 1H, J=1.5 Hz), 7.64 (d, 1H, J=8.6 Hz), 7.47 (dd, 1H, J=8.6, 1.5 Hz), 6.69 (s, 1H), 2.37 (s, 3H).

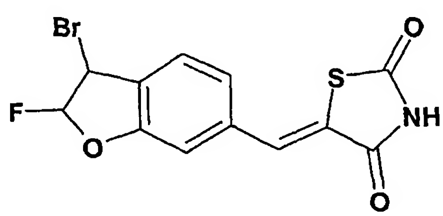
Example 110: 5-(2-Carboxymethyl-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 5-[1,3]Dioxolan-2-yl-benzofuran-2-carboxylic acid methyl ester (intermediate 73) and 1,3-thiazolidine-2,4-dione, the title compound was obtained after purification on reverse phase HPLC (solvents gradient H_2O/CH_3CN 0.1% TFA).

HPLC: 3.32 min, 92.06%. LC-MS: M/Z ESI: 1.51 min, 302.19 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.52 (sl, 1H), 7.97 (d, 1H, J=1.5 Hz), 7.82 (m, 3H), 7.69 (dd, 1H, J=8.6, 1.5 Hz), 3.90 (s, 3H).

Example 111: 5-(3-Bromo-2-fluoro-2,3-dihydro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione

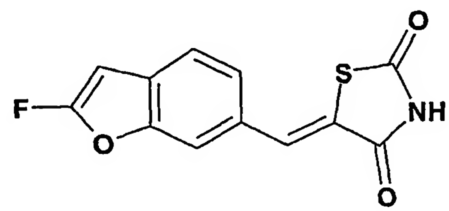


Following the general method as outlined in Example 1, starting from 3-Bromo-2-fluoro-benzofuran-5-carbaldehyde (intermediate 74) and 1,3-thiazolidine-2,4-dione, the title compound was obtained after purification on reverse phase HPLC (solvents gradient H_2O/CH_3CN 0.1% TFA).

HPLC: 3.66 min, 92.37%. LC-MS: M/Z ESI: 1.56 min, 343.09 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.82 (sl, 1H), 8.00 (d, 1H, J=1.8 Hz), 7.88 (dd, 1H, J=8.5, 1.8 Hz), 7.55 (d, 1H,

J=8.5 Hz), 7.03 (d, 1H, $^{2}J_{H-F}$=59.5 Hz), 6.20 (d, 1H, $^{3}J_{H-F}$=15.3 Hz). ^{19}F NMR: (DMSO-d6) δ-114.66.

Example 112: 5-(2-Fluoro-benzofuran-6-ylmethylene)-thiazolidine-2,4-dione



Following the general method as outlined in Example 1, starting from 2-Fluoro-5-[1,3]dioxolan-2-yl-benzofuran (intermediate 75) and 1,3-thiazolidine-2,4-dione, the title compound was obtained after purification on reverse phase HPLC (solvents gradient H_2O/CH_3CN 0.1% TFA).

HPLC: 3.67 min, 99.47%. LC-MS: M/Z ESI: 1.51 min, 262.14 (M-1). ^{1}H NMR: (DMSO-d6) δ 12.04 (sl, 1H), 7.89 (d, 1H, J=1.5 Hz), 7.83 (d, 1H, J=1.5 Hz), 7.73 (d, 1H, J=8.6 Hz), 7.55 (dd, 1H, J=8.6, 1.5 Hz), 6.47 (d, 1H, $^{3}J_{H-F}$=6.4 Hz). ^{19}F NMR: (DMSO-d6) δ-111.28, -112.18.

Example 113 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets

A compound of formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg) of active azolidinone compound per tablet) in a tablet press.

Formulation 2 – Capsules

A compound of formula (I) is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active azolidinone compound per capsule).

Formulation 3 – Liquid

A compound of formula (I) (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

A compound of formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active azolidinone compound) in a tablet press.

Formulation 5 – Injection

A compound of formula (I) is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 114 : Biological assays

The compounds of the present invention may be subjected to the following assays:

a) High Throughput PI3K lipid kinase assay (binding assay):

The assay combines the scintillation proximity assay technology (SPA, Amersham) with the capacity of neomycin (a polycationic antibiotic) to bind phospholipids with high

affinity and specificity. The Scintillation Proximity Assay is based on the properties of weakly emitting isotopes (such as ^{3}H, ^{125}I, ^{33}P). Coating SPA beads with neomycin allows the detection of phosphorylated lipid substrates after incubation with recombinant PI3K and radioactive ATP in the same well, by capturing the radioactive phospholipids to the SPA beads through their specific binding to neomycin.

To a 384 wells MTP containing 5 µl of the test compound of formula (I) (solubilized in 6% DMSO; to yield a concentration of 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.001 µM of the test compound), the following assay components are added. **1)** 5 µl (58 ng) of Human recombinant GST-PI3Kγ (in Hepes 40 mM, pH 7.4, DTT 1 mM and ethylenglycol 5%) **2)** 10 µl of lipid micelles and **3)** 10 µl of Kinase buffer ([^{33}P]γ-ATP 45µM/60nCi, $MgCl_2$ 30mM, DTT 1mM, β-Glycerophosphate 1mM, Na_3VO_4 100 µM, Na Cholate 0.3 %, in Hepes 40 mM, pH 7.4). After incubation at room temperature for 180 minutes, with gentle agitation, the reaction is stopped by addition of 60 µl of a solution containing 100 µg of neomycin-coated PVT SPA beads in PBS containing ATP 10mM and EDTA 5mM. The assay is further incubated at room temperature for 60 minutes with gentle agitation to allow binding of phospholipids to neomycin-SPA beads. After precipitation of the neomycin-coated PVT SPA beads for 5 minutes at 1500 x g, radioactive *PtdIns(3)P* is quantified by scintillation counting in a Wallac MicroBeta ™ plate counter.

The values indicated in respect of PI3K γ refer to the IC_{50} (µM), i.e. the amount necessary to achieve 50% inhibition of said target. Said values show a considerable potency of the azolidinone-vinyl fused-benzene compounds with regard to PI3Kγ.

The tested compounds according to formula (I) display an inhibition (IC_{50}) with regard to PI3Kγ of less than 2 µM, more preferred equal or less than 1 µM.

Examples of inhibitory activities for test compounds 41, 61, 66, 73, 103, 107 and 110 as set out in Table 1.

Example No	*PI3Kγ, IC_{50} (μ M)*
41	< 1
61	< 1
66	< 1
73	< 1
103	< 1
107	< 1
110	< 1

Table 1: IC_{50} values of azolidinone-vinyl fused-benzene derivatives against PI3Kγ.

b) Cell based ELISA to monitor PI3K inhibition:

Measurement of Akt/PKB phosphorylation in macrophages after stimulation with C5a: Raw 264: Raw 264-7 macrophages (cultured in DMEM-F12 medium containing 10% Fetal Calf serum and antibiotics) are plated at 20'000 cells/well in a 96 MTP 24 h before cell stimulation. Previous to the stimulation with 50 nM of Complement 5a (C5a; which is a well known chemokine which stimulates the used cells) during 5 minutes, Cells are serum starved for 2h, and pretreated with inhibitors for 20 minutes. After stimulation cells are fixed in 4% formaldehyde for 20 minutes and washed 3 times in PBS containing 1% Triton X-100 (PBS/Triton). Endogenous peroxidase is blocked by a 20 minutes incubation in 0.6% H_2O_2 and 0.1% Sodium Azide in PBS/Triton and washed 3 times in PBS/Triton. Cells are then blocked by 60 minutes incubation with 10% fetal calf serum in PBS/Triton. Next, phosphorylated Akt/PKB is detected by an overnight incubation at 4°C with first antibody (anti phospho Serine 473 Akt IHC, Cell Signaling) diluted 800-fold in PBS/Triton, containing 5% bovine serum albumin (BSA). After 3 washes in PBS/Triton, cells are incubated for 60 minutes with a peroxidase conjugated goat-anti-rabbit antibody (1/400 dilution in PBS/Triton, containing 5% BSA), washed 3 times in PBS/Triton, and 2 times in PBS and further incubated in 100 μl of substrate reagent solution (R&D) for 20 minutes.

The reaction is stopped by addition of 50 µl of 1 M H_2SO_4 and absorbance is read at 450 nm.

The values indicated reflect the percentage of inhibition of AKT phoshorylation as compared to basal level. Said values show a clear effect of the azolidinone-vinyl fused-benzene compounds on the activation of AKT phosphorylation in macrophages.

Compounds of examples 1, 19, 66 and 107, when used at 10µM completely (about 100%) inhibit C5a-mediated AKT phosophorylation. Examples 17, 19 or 73, when used at 1µM, inhibit 95% of the C5a-mediated AKT-phosphorylation.